

ANNEX

List of Largest Pharmaceutical Settlements

List of Largest Pharmaceutical Settlements

The following is a big list of the 20 largest settlements reached between the United States Department of Justice and pharmaceutical companies from 1991 to 2012, ordered by the size of the total settlement.

The settlement amount includes both the civil (False Claims Act) settlement and criminal fine.

Glaxo's \$3 Billion settlement included the largest civil False Claims Act settlement on record, and Pfizer's \$2.3 Billion (\$3.5 Billion in 2022) settlement including a record-breaking \$1.3 Billion criminal fine.

Legal claims against the pharmaceutical industry have varied widely over the past two decades, including Medicare and Medicaid fraud, off-label promotion, and inadequate manufacturing practices.

With respect to off-label promotion, specifically, a federal court recognized off-label promotion as a violation of the False Claims Act for the first time in *Franklin v. Parke-Davis*, leading to a \$430 million settlement.

Year	Company	Settlement	Violation(s)	Product(s)	Laws violated
2012	GlaxoSmithKline	\$3 Billion (\$1B criminal, \$2B civil)	Criminal: Off-label promotion, failure to disclose safety data. Civil: paying kickbacks to physicians, making false and misleading statements concerning the safety of Avandia, reporting false best prices and underpaying rebates owed under the Medicaid Drug Rebate Program	Avandia (not providing safety data), Wellbutrin, Paxil (promotion of paediatric use), Advair, Lamictal, Zofran, Imitrex, Lotronex, Flovent, Valtrex	False Claims Act, FDCA
2009	Pfizer	\$2.3 Billion	Off-label promotion, kickbacks	Bextra, Geodon, Zyvox, Lyrica	False Claims Act, FDCA
2013	Johnson & Johnson	\$2.2 Billion	Off-label promotion, kickbacks	Risperdal, Invega, Nesiritide	False Claims Act, FDCA
2012	Abbott	\$1.5 Billion	Off-label promotion	Depakote	False Claims

Year	Company	Settlement	Violation(s)	Product(s)	Laws violated
	Laboratories				Act, FDCA
2009	Eli Lilly	\$1.4 Billion	Off-label promotion	Zyprexa	False Claims Act, FDCA
2001	TAP Pharmaceutical Products	\$875 Million	Medicare fraud, kickbacks	Lupron	False Claims Act, Prescription Drug Marketing Act
2012	Amgen	\$762 Million	Off-label promotion, kickbacks	Aranesp	False Claims Act, FDCA
2010	GlaxoSmithKline	\$750 Million	Poor manufacturing practices	Kytril, Bactroban, Paxil CR, Avandamet	False Claims Act, FDCA
2005	Serono	\$704 Million	Off-label promotion, kickbacks, monopolistic practices	Serostim	False Claims Act
2008	Merck	\$650 Million	Medicare fraud, kickbacks	Zocor, Vioxx, Pepsid	False Claims Act, Medicaid Rebate Statute
2007	Purdue Pharma	\$601 Million	Off-label promotion	Oxycontin	False Claims Act
2010	Allergan	\$600 Million	Off-label promotion	Botox	False Claims Act, FDCA
2010	AstraZeneca	\$520 Million	Off-label promotion, kickbacks	Seroquel	False Claims Act
2007	Bristol-Myers Squibb	\$515 Million	Off-label promotion, kickbacks, Medicare fraud	Abilify, Serzone	False Claims Act, FDCA
2002	Schering-Plough	\$500 Million	Poor manufacturing practices	Claritin	FDA Current Good Manufacturing Practices
2006	Mylan	\$465 Million	Misclassification under the Medicaid Drug Rebate Program	EpiPen (epinephrine)	False Claims Act
2006	Schering-Plough	\$435 Million	Off-label promotion, kickbacks, Medicare fraud	Temodar, Intron A, K-Dur, Claritin Reditabs	False Claims Act, FDCA

Year	Company	Settlement	Violation(s)	Product(s)	Laws violated
2004	Pfizer	\$430 Million	Off-label promotion	Neurontin	False Claims Act, FDCA
2008	Cephalon	\$425 Million	Off-label promotion	Actiq, Gabitril, Provigil	False Claims Act, FDCA
2010	Novartis	\$423 Million	Off-label promotion, kickbacks	Trileptal	False Claims Act, FDCA
2003	AstraZeneca	\$355 Million	Medicare fraud	Zoladex	Prescription Drug Marketing Act
2004	Schering-Plough	\$345 Million	Medicare fraud, kickbacks	Claritin	False Claims Act, Anti-Kickback Statute

- in “Wikipedia”, 9 May 2022.

ANNEX

List of Covid-19 Vaccine Side Effects

5.3.6 CUMULATIVE ANALYSIS OF POST-AUTHORIZATION ADVERSE EVENT REPORTS OF PF-07302048 (BNT162B2) RECEIVED THROUGH 28-FEB-2021

Report Prepared by:

Worldwide Safety

Pfizer

The information contained in this document is proprietary and confidential. Any disclosure, reproduction, distribution, or other dissemination of this information outside of Pfizer, its Affiliates, its Licensees, or Regulatory Agencies is strictly prohibited. Except as may be otherwise agreed to in writing, by accepting or reviewing these materials, you agree to hold such information in confidence and not to disclose it to others (except where required by applicable law), nor to use it for unauthorized purposes.

TABLE OF CONTENTS

LIST OF TABLES	3
LIST OF FIGURES	3
APPENDICES	3
LIST OF ABBREVIATIONS.....	4
1. INTRODUCTION	5
2. METHODOLOGY	5
3. RESULTS	6
3.1. Safety Database	6
3.1.1. General Overview	6
3.1.2. Summary of Safety Concerns in the US Pharmacovigilance Plan	9
3.1.3. Review of Adverse Events of Special Interest (AESIs)	16
3.1.4. Medication error	26
4. DISCUSSION	28
5. SUMMARY AND CONCLUSION	29

LIST OF TABLES

Table 1.	General Overview: Selected Characteristics of All Cases Received During the Reporting Interval.....	7
Table 2.	Events Reported in $\geq 2\%$ Cases.....	8
Table 3.	Safety concerns	9
Table 4.	Important Identified Risk.....	10
Table 5.	Important Potential Risk	11
Table 6.	Description of Missing Information	12
Table 7.	AESIs Evaluation for BNT162b2	16
Table 8.	ME PTs by seriousness with or without harm co-association (Through 28 February 2021)	27

LIST OF FIGURES

Figure 1.	Total Number of 13vPnC AEs by System Organ Classes and Event Seriousness	8
-----------	--	---

APPENDICES

APPENDIX 1 LIST OF ADVERSE EVENTS OF SPECIAL INTEREST	30
---	----

LIST OF ABBREVIATIONS

Acronym	Term
AE	adverse event
AESI	adverse event of special interest
BC	Brighton Collaboration
CDC	Centers for Disease Control and Prevention
COVID-19	coronavirus disease 2019
DLP	data lock point
EUA	emergency use authorisation
HLGT	(MedDRA) High Group Level Term
HLT	(MedDRA) High Level Term
MAH	marketing authorisation holder
MedDRA	medical dictionary for regulatory activities
MHRA	Medicines and Healthcare products Regulatory Agency
PCR	Polymerase Chain Reaction
PT	(MedDRA) Preferred Term
PVP	pharmacovigilance plan
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
RSI	reference safety information
TME	targeted medically event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMQ	standardised MedDRA query
SOC	(MedDRA) System Organ Class
UK	United Kingdom
US	United States
VAED	vaccine-associated enhanced disease
VAERD	vaccine-associated enhanced respiratory disease
VAERS	vaccine adverse event reporting system

1. INTRODUCTION

Reference is made to the Request for Comments and Advice submitted 04 February 2021 regarding Pfizer/BioNTech's proposal for the clinical and post-authorization safety data package for the Biologics License Application (BLA) for our investigational COVID-19 Vaccine (BNT162b2). Further reference is made to the Agency's 09 March 2021 response to this request, and specifically, the following request from the Agency.

“Monthly safety reports primarily focus on events that occurred during the reporting interval and include information not relevant to a BLA submission such as line lists of adverse events by country. We are most interested in a cumulative analysis of post-authorization safety data to support your future BLA submission. Please submit an integrated analysis of your cumulative post-authorization safety data, including U.S. and foreign post-authorization experience, in your upcoming BLA submission. Please include a cumulative analysis of the Important Identified Risks, Important Potential Risks, and areas of Important Missing Information identified in your Pharmacovigilance Plan, as well as adverse events of special interest and vaccine administration errors (whether or not associated with an adverse event). Please also include distribution data and an analysis of the most common adverse events. In addition, please submit your updated Pharmacovigilance Plan with your BLA submission.”

This document provides an integrated analysis of the cumulative post-authorization safety data, including U.S. and foreign post-authorization adverse event reports received through 28 February 2021.

2. METHODOLOGY

Pfizer is responsible for the management post-authorization safety data on behalf of the MAH BioNTech according to the Pharmacovigilance Agreement in place. Data from BioNTech are included in the report when applicable.

Pfizer's safety database contains cases of AEs reported spontaneously to Pfizer, cases reported by the health authorities, cases published in the medical literature, cases from Pfizer-sponsored marketing programs, non-interventional studies, and cases of serious AEs reported from clinical studies regardless of causality assessment.

The limitations of post-marketing adverse drug event reporting should be considered when interpreting these data:

- Reports are submitted voluntarily, and the magnitude of underreporting is unknown. Some of the factors that may influence whether an event is reported include: length of time since marketing, market share of the drug, publicity about a drug or an AE, seriousness of the reaction, regulatory actions, awareness by health professionals and consumers of adverse drug event reporting, and litigation.
- Because many external factors influence whether or not an AE is reported, the spontaneous reporting system yields reporting proportions not incidence rates. As a result, it is generally not appropriate to make between-drug comparisons using these

proportions; the spontaneous reporting system should be used for signal detection rather than hypothesis testing.

- In some reports, clinical information (such as medical history, validation of diagnosis, time from drug use to onset of illness, dose, and use of concomitant drugs) is missing or incomplete, and follow-up information may not be available.
- An accumulation of adverse event reports (AERs) does not necessarily indicate that a particular AE was caused by the drug; rather, the event may be due to an underlying disease or some other factor(s) such as past medical history or concomitant medication.
- Among adverse event reports received into the Pfizer safety database during the cumulative period, only those having a complete workflow cycle in the safety database (meaning they progressed to Distribution or Closed workflow status) are included in the monthly SMSR. This approach prevents the inclusion of cases that are not fully processed hence not accurately reflecting final information. Due to the large numbers of spontaneous adverse event reports received for the product, the MAH has prioritised the processing of serious cases, in order to meet expedited regulatory reporting timelines and ensure these reports are available for signal detection and evaluation activity. The increased volume of reports has not impacted case processing for serious reports, and compliance metrics continue to be monitored weekly with prompt action taken as needed to maintain compliance with expedited reporting obligations. Non-serious cases are entered into the safety database no later than 4 calendar days from receipt. Entrance into the database includes the coding of all adverse events; this allow for a manual review of events being received but may not include immediate case processing to completion. Non-serious cases are processed as soon as possible and no later than 90 days from receipt. Pfizer has also taken a multiple actions to help alleviate the large increase of adverse event reports. This includes significant technology enhancements, and process and workflow solutions, as well as increasing the number of data entry and case processing colleagues. To date, Pfizer has onboarded approximately (b) (4) additional full-time employees (FTEs). More are joining each month with an expected total of more than (b) (4) additional resources by the end of June 2021.

3. RESULTS

3.1. Safety Database

3.1.1. General Overview

It is estimated that approximately (b) (4) doses of BNT162b2 were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 28 February 2021.

Cumulatively, through 28 February 2021, there was a total of 42,086 case reports (25,379 medically confirmed and 16,707 non-medically confirmed) containing 158,893 events. Most cases (34,762) were received from United States (13,739), United Kingdom (13,404) Italy (2,578), Germany (1913), France (1506), Portugal (866) and Spain (756); the remaining 7,324 were distributed among 56 other countries.

Table 1 below presents the main characteristics of the overall cases.

Table 1. General Overview: Selected Characteristics of All Cases Received During the Reporting Interval

Characteristics		Relevant cases (N=42086)
Gender:	Female	29914
	Male	9182
	No Data	2990
Age range (years): 0.01 -107 years Mean = 50.9 years n = 34952	≤ 17	175 ^a
	18-30	4953
	31-50	13886
	51-64	7884
	65-74	3098
	≥ 75	5214
	Unknown	6876
Case outcome:	Recovered/Recovering	19582
	Recovered with sequelae	520
	Not recovered at the time of report	11361
	Fatal	1223
	Unknown	9400

a. in 46 cases reported age was <16-year-old and in 34 cases <12-year-old.

As shown in [Figure 1](#), the System Organ Classes (SOCs) that contained the greatest number ($\geq 2\%$) of events, in the overall dataset, were General disorders and administration site conditions (51,335 AEs), Nervous system disorders (25,957), Musculoskeletal and connective tissue disorders (17,283), Gastrointestinal disorders (14,096), Skin and subcutaneous tissue disorders (8,476), Respiratory, thoracic and mediastinal disorders (8,848), Infections and infestations (4,610), Injury, poisoning and procedural complications (5,590), and Investigations (3,693).

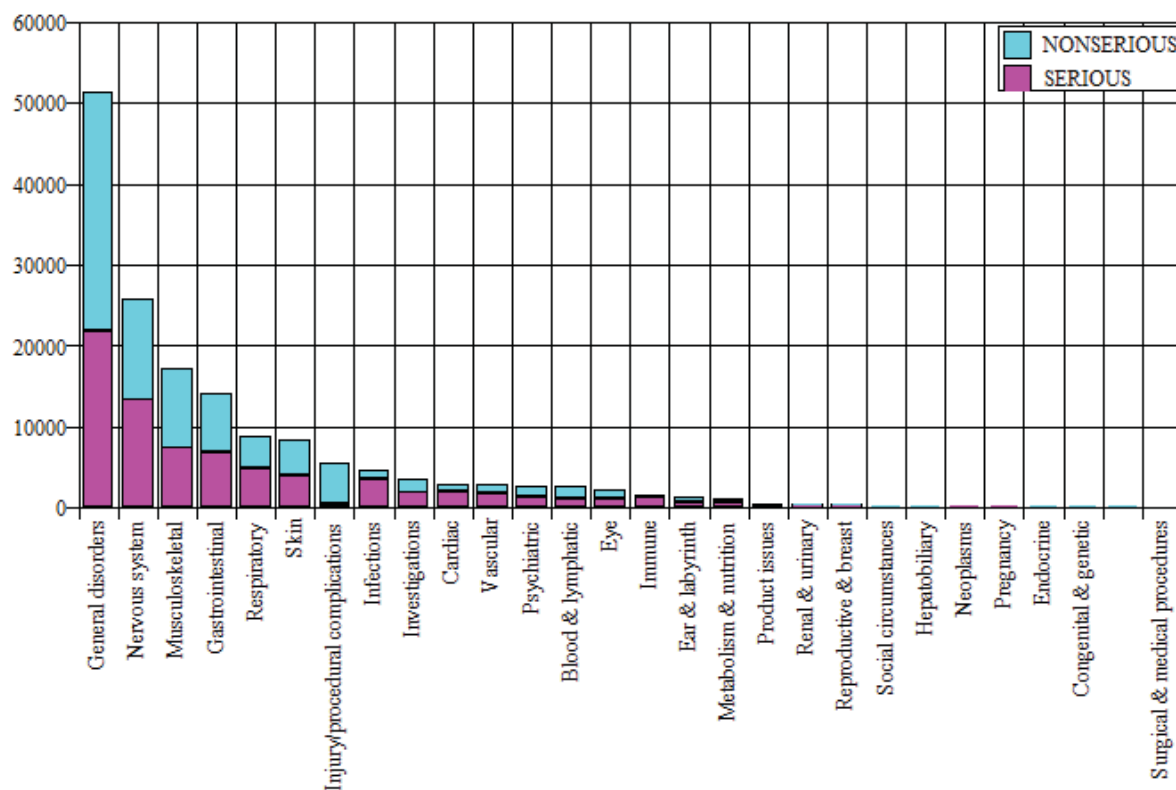
Figure 1. Total Number of BNT162b2 AEs by System Organ Classes and Event Seriousness

Table 2 shows the most commonly ($\geq 2\%$) reported MedDRA (v. 23.1) PTs in the overall dataset (through 28 February 2021),

Table 2. Events Reported in $\geq 2\%$ Cases

MedDRA SOC	MedDRA PT	Cumulatively Through 28 February 2021 AEs (AERP%) N = 42086
Blood and lymphatic system disorders		
	Lymphadenopathy	1972 (4.7%)
Cardiac disorders		
	Tachycardia	1098 (2.6%)
Gastrointestinal disorders		
	Nausea	5182 (12.3%)
	Diarrhoea	1880 (4.5%)
	Vomiting	1698 (4.0%)
General disorders and administration site conditions		
	Pyrexia	7666 (18.2%)
	Fatigue	7338 (17.4%)
	Chills	5514 (13.1%)
	Vaccination site pain	5181 (12.3%)

Table 2. Events Reported in $\geq 2\%$ Cases

		Cumulatively Through 28 February 2021
MedDRA SOC	MedDRA PT	AEs (AERP%) N = 42086
	Pain	3691 (8.8%)
	Malaise	2897 (6.9%)
	Asthenia	2285 (5.4%)
	Drug ineffective	2201 (5.2%)
	Vaccination site erythema	930 (2.2%)
	Vaccination site swelling	913 (2.2%)
	Influenza like illness	835 (2%)
Infections and infestations		
	COVID-19	1927 (4.6%)
Injury, poisoning and procedural complications		
	Off label use	880 (2.1%)
	Product use issue	828 (2.0%)
Musculoskeletal and connective tissue disorders		
	Myalgia	4915 (11.7%)
	Pain in extremity	3959 (9.4%)
	Arthralgia	3525 (8.4%)
Nervous system disorders		
	Headache	10131 (24.1%)
	Dizziness	3720 (8.8%)
	Paraesthesia	1500 (3.6%)
	Hypoaesthesia	999 (2.4%)
Respiratory, thoracic and mediastinal disorders		
	Dyspnoea	2057 (4.9%)
	Cough	1146 (2.7%)
	Oropharyngeal pain	948 (2.3%)
Skin and subcutaneous tissue disorders		
	Pruritus	1447 (3.4%)
	Rash	1404 (3.3%)
	Erythema	1044 (2.5%)
	Hyperhidrosis	900 (2.1%)
	Urticaria	862 (2.1%)
Total number of events		93473

3.1.2. Summary of Safety Concerns in the US Pharmacovigilance Plan**Table 3. Safety concerns**

Important identified risks	Anaphylaxis
Important potential risks	Vaccine-Associated Enhanced Disease (VAED), Including Vaccine-associated Enhanced Respiratory Disease (VAERD)
Missing information	Use in Pregnancy and lactation Use in Paediatric Individuals <12 Years of Age Vaccine Effectiveness

Table 4. Important Identified Risk

Topic	Description														
Important Identified Risk	Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)														
Anaphylaxis	Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 28 February 2021, 1833 potentially relevant cases were retrieved from the Anaphylactic reaction SMQ (Narrow and Broad) search strategy, applying the MedDRA algorithm. These cases were individually reviewed and assessed according to Brighton Collaboration (BC) definition and level of diagnostic certainty as shown in the Table below: <table border="1"> <thead> <tr> <th>Brighton Collaboration Level</th><th>Number of cases</th></tr> </thead> <tbody> <tr> <td>BC 1</td><td>290</td></tr> <tr> <td>BC 2</td><td>311</td></tr> <tr> <td>BC 3</td><td>10</td></tr> <tr> <td>BC 4</td><td>391</td></tr> <tr> <td>BC 5</td><td>831</td></tr> <tr> <td><i>Total</i></td><td>1833</td></tr> </tbody> </table> Level 1 indicates a case with the highest level of diagnostic certainty of anaphylaxis, whereas the diagnostic certainty is lowest for Level 3. Level 4 is defined as “reported event of anaphylaxis with insufficient evidence to meet the case definition” and Level 5 as not a case of anaphylaxis. There were 1002 cases (54.0% of the potentially relevant cases retrieved), 2958 potentially relevant events, from the Anaphylactic reaction SMQ (Broad and Narrow) search strategy, meeting BC Level 1 to 4: Country of incidence: UK (261), US (184), Mexico (99), Italy (82), Germany (67), Spain (38), France (36), Portugal (22), Denmark (20), Finland, Greece (19 each), Sweden (17), Czech Republic , Netherlands (16 each), Belgium, Ireland (13 each), Poland (12), Austria (11); the remaining 57 cases originated from 15 different countries. Relevant event seriousness: Serious (2341), Non-Serious (617); Gender: Females (876), Males (106), Unknown (20); Age (n=961) ranged from 16 to 98 years (mean = 54.8 years, median = 42.5 years); Relevant even outcome^a: fatal (9)^b, resolved/resolving (1922), not resolved (229), resolved with sequelae (48), unknown (754); Most frequently reported relevant PTs (≥2%), from the Anaphylactic reaction SMQ (Broad and Narrow) search strategy: Anaphylactic reaction (435), Dyspnoea (356), Rash (190), Pruritus (175), Erythema (159), Urticaria (133), Cough (115), Respiratory distress, Throat tightness (97 each), Swollen tongue (93), Anaphylactic shock (80), Hypotension (72), Chest discomfort (71), Swelling face (70), Pharyngeal swelling (68), and Lip swelling (64). Conclusion: Evaluation of BC cases Level 1 - 4 did not reveal any significant new safety information. Anaphylaxis is appropriately described in the product labeling as are non-anaphylactic hypersensitivity events. Surveillance will continue.	Brighton Collaboration Level	Number of cases	BC 1	290	BC 2	311	BC 3	10	BC 4	391	BC 5	831	<i>Total</i>	1833
Brighton Collaboration Level	Number of cases														
BC 1	290														
BC 2	311														
BC 3	10														
BC 4	391														
BC 5	831														
<i>Total</i>	1833														

^a Different clinical outcome may be reported for an event that occurred more than once to the same individual.

^b There were 4 individuals in the anaphylaxis evaluation who died on the same day they were vaccinated. Although these patients experienced adverse events (9) that are potential symptoms of anaphylaxis, they all had serious underlying medical conditions, and one individual appeared to also have COVID-19 pneumonia, that likely contributed to their deaths

Table 5. Important Potential Risk

Topic	Description
Important Potential Risk	Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)
Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)	No post-authorized AE reports have been identified as cases of VAED/VAERD, therefore, there is no observed data at this time. An expected rate of VAED is difficult to establish so a meaningful observed/expected analysis cannot be conducted at this point based on available data. The feasibility of conducting such an analysis will be re-evaluated on an ongoing basis as data on the virus grows and the vaccine safety data continues to accrue. The search criteria utilised to identify potential cases of VAED for this report includes PTs indicating a lack of effect of the vaccine and PTs potentially indicative of severe or atypical COVID-19^a. Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 28 February 2021, 138 cases [0.33% of the total PM dataset], reporting 317 potentially relevant events were retrieved: Country of incidence: UK (71), US (25), Germany (14), France, Italy, Mexico, Spain, (4 each), Denmark (3); the remaining 9 cases originated from 9 different countries; Cases Seriousness: 138; Seriousness criteria for the total 138 cases: Medically significant (71, of which 8 also serious for disability), Hospitalization required (non-fatal/non-life threatening) (16, of which 1 also serious for disability), Life threatening (13, of which 7 were also serious for hospitalization), Death (38). Gender: Females (73), Males (57), Unknown (8); Age (n=132) ranged from 21 to 100 years (mean = 57.2 years, median = 59.5); Case outcome: fatal (38), resolved/resolving (26), not resolved (65), resolved with sequelae (1), unknown (8); Of the 317 relevant events, the most frequently reported PTs ($\geq 2\%$) were: Drug ineffective (135), Dyspnoea (53), Diarrhoea (30), COVID-19 pneumonia (23), Vomiting (20), Respiratory failure (8), and Seizure (7). Conclusion: VAED may present as severe or unusual clinical manifestations of COVID-19. Overall, there were 37 subjects with suspected COVID-19 and 101 subjects with confirmed COVID-19 following one or both doses of the vaccine; 75 of the 101 cases were severe, resulting in hospitalisation, disability, life-threatening consequences or death. None of the 75 cases could be definitively considered as VAED/VAERD. In this review of subjects with COVID-19 following vaccination, based on the current evidence, VAED/VAERD remains a theoretical risk for the vaccine. Surveillance will continue.

a. Search criteria: Standard Decreased Therapeutic Response Search AND PTs Dyspnoea; Tachypnoea; Hypoxia; COVID 19 pneumonia; Respiratory Failure; Acute Respiratory Distress Syndrome; Cardiac Failure; Cardiogenic shock; Acute myocardial infarction; Arrhythmia; Myocarditis; Vomiting; Diarrhoea; Abdominal pain; Jaundice; Acute hepatic failure; Deep vein thrombosis; Pulmonary embolism; Peripheral Ischaemia; Vasculitis; Shock; Acute kidney injury; Renal failure; Altered state of consciousness; Seizure; Encephalopathy; Meningitis; Cerebrovascular accident; Thrombocytopenia; Disseminated intravascular coagulation; Chillblains; Erythema multiforme; Multiple organ dysfunction syndrome; Multisystem inflammatory syndrome in children.

Table 6. Description of Missing Information

Topic	Description
Missing Information	Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)
Use in Pregnancy and lactation	- Number of cases: 413^a (0.98% of the total PM dataset); 84 serious and 329 non-serious; - Country of incidence: US (205), UK (64), Canada (31), Germany (30), Poland (13), Israel (11); Italy (9), Portugal (8), Mexico (6), Estonia, Hungary and Ireland, (5 each), Romania (4), Spain (3), Czech Republic and France (2 each), the remaining 10 cases were distributed among 10 other countries. Pregnancy cases: 274 cases including: 270 mother cases and 4 foetus/baby cases representing 270 unique pregnancies (the 4 foetus/baby cases were linked to 3 mother cases; 1 mother case involved twins). - Pregnancy outcomes for the 270 pregnancies were reported as spontaneous abortion (23), outcome pending (5), premature birth with neonatal death, spontaneous abortion with intrauterine death (2 each), spontaneous abortion with neonatal death, and normal outcome (1 each). No outcome was provided for 238 pregnancies (note that 2 different outcomes were reported for each twin, and both were counted). 146 non-serious mother cases reported exposure to vaccine in utero without the occurrence of any clinical adverse event. The exposure PTs coded to the PTs Maternal exposure during pregnancy (111), Exposure during pregnancy (29) and Maternal exposure timing unspecified (6). Trimester of exposure was reported in 21 of these cases: 1st trimester (15 cases), 2nd trimester (7), and 3rd trimester (2). 124 mother cases, 49 non-serious and 75 serious, reported clinical events, which occurred in the vaccinated mothers. Pregnancy related events reported in these cases coded to the PTs Abortion spontaneous (25), Uterine contraction during pregnancy, Premature rupture of membranes, Abortion, Abortion missed, and Foetal death (1 each). Other clinical events which occurred in more than 5 cases coded to the PTs Headache (33), Vaccination site pain (24), Pain in extremity and Fatigue (22 each), Myalgia and Pyrexia (16 each), Chills (13) Nausea (12), Pain (11), Arthralgia (9), Lymphadenopathy and Drug ineffective (7 each), Chest pain, Dizziness and Asthenia (6 each), Malaise and COVID-19 (5 each). Trimester of exposure was reported in 22 of these cases: 1st trimester (19 cases), 2nd trimester (1 case), 3rd trimester (2 cases). 4 serious foetus/baby cases reported the PTs Exposure during pregnancy, Foetal growth restriction, Maternal exposure during pregnancy, Premature baby (2 each), and Death neonatal (1). Trimester of exposure was reported for 2 cases (twins) as occurring during the 1st trimester. Breast feeding baby cases: 133, of which: 116 cases reported exposure to vaccine during breastfeeding (PT Exposure via breast milk) without the occurrence of any clinical adverse events; 17 cases, 3 serious and 14 non-serious, reported the following clinical events that occurred in the infant/child exposed to vaccine via breastfeeding: Pyrexia (5), Rash (4), Infant irritability (3), Infantile vomiting, Diarrhoea, Insomnia, and Illness (2 each), Poor feeding infant, Lethargy, Abdominal discomfort, Vomiting, Allergy to vaccine, Increased appetite, Anxiety, Crying, Poor quality sleep, Eructation, Agitation, Pain and Urticaria (1 each). Breast feeding mother cases (6): 1 serious case reported 3 clinical events that occurred in a mother during breast feeding (PT Maternal exposure during breast feeding); these events coded to the PTs Chills, Malaise, and Pyrexia 1 non-serious case reported with very limited information and without associated AEs.

Table 6. Description of Missing Information

Topic	Description
Missing Information	Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086) In 4 cases (3 non-serious; 1 serious) Suppressed lactation occurred in a breast feeding women with the following co-reported events: Pyrexia (2), Paresis, Headache, Chills, Vomiting, Pain in extremity, Arthralgia, Breast pain, Scar pain, Nausea, Migraine, Myalgia, Fatigue and Breast milk discolouration (1 each). Conclusion: There were no safety signals that emerged from the review of these cases of use in pregnancy and while breast feeding.
Use in Paediatric Individuals <12 Years of Age	<u>Paediatric individuals <12 years of age</u> - Number of cases: 34^d (0.1% of the total PM dataset), indicative of administration in paediatric subjects <12 years of age; - Country of incidence: UK (29), US (3), Germany and Andorra (1 each); - Cases Seriousness: Serious (24), Non-Serious (10); - Gender: Females (25), Males (7), Unknown (2); - Age (n=34) ranged from 2 months to 9 years, mean = 3.7 years, median = 4.0; - Case outcome: resolved/resolving (16), not resolved (13), and unknown (5). - Of the 132 reported events, those reported more than once were as follows: Product administered to patient of inappropriate age (27, see Medication Error), Off label use (11), Pyrexia (6), Product use issue (5), Fatigue, Headache and Nausea (4 each), Vaccination site pain (3), Abdominal pain upper, COVID-19, Facial paralysis, Lymphadenopathy, Malaise, Pruritus and Swelling (2 each). Conclusion: No new significant safety information was identified based on a review of these cases compared with the non-paediatric population.
Vaccine Effectiveness	Company conventions for coding cases indicative of lack of efficacy: The coding conventions for lack of efficacy in the context of administration of the COVID-19 vaccine were revised on 15 February 2021, as shown below: - PT “Vaccination failure” is coded when ALL of the following criteria are met: - The subject has received the series of two doses per the dosing regimen in local labeling. - At least 7 days have elapsed since the second dose of vaccine has been administered. - The subject experiences SARS-CoV-2 infection (confirmed laboratory tests). - PT “Drug ineffective” is coded when either of the following applies: - The infection is not confirmed as SARS-CoV-2 through laboratory tests (irrespective of the vaccination schedule). This includes scenarios where LOE is stated or implied, e.g., “the vaccine did not work”, “I got COVID-19”. - It is unknown: - Whether the subject has received the series of two doses per the dosing regimen in local labeling; - How many days have passed since the first dose (including unspecified number of days like “a few days”, “some days”, etc.); - If 7 days have passed since the second dose; - The subject experiences a vaccine preventable illness 14 days after receiving the first dose up to and through 6 days after receipt of the second dose. Note: after the immune system as had sufficient time (14 days) to respond to the vaccine, a report of COVID-19 is considered a potential lack of efficacy even if the vaccination course is not complete. Summary of the coding conventions for onset of vaccine preventable disease versus the vaccination date:

Table 6. Description of Missing Information

Topic	Description		
Missing Information	Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)		
	1st dose (day 1-13)	From day 14 post 1st dose to day 6 post 2nd dose	Day 7 post 2nd dose
	Code only the events describing the SARS-CoV-2 infection	Code “Drug ineffective”	Code “Vaccination failure”
	Scenario Not considered LOE	Scenario considered LOE as “Drug ineffective”	Scenario considered LOE as “Vaccination failure”
	Lack of efficacy cases - Number of cases: 1665^b (3.9 % of the total PM dataset) of which 1100 were medically confirmed and 565 non medically confirmed; - Number of lack of efficacy events: 1665 [PT: Drug ineffective (1646) and Vaccination failure (19)^f]. - Country of incidence: US (665), UK (405), Germany (181), France (85), Italy (58), Romania (47), Belgium (33), Israel (30), Poland (28), Spain (21), Austria (18), Portugal (17), Greece (15), Mexico (13), Denmark (8), Canada (7), Hungary, Sweden and United Arab Emirates (5 each), Czech Republic (4), Switzerland (3); the remaining 12 cases originated from 9 different countries. - COVID-19 infection was suspected in 155 cases, confirmed in 228 cases, in 1 case it was reported that the first dose was not effective (no other information). - COVID-19 infection (suspected or confirmed) outcome was reported as resolved/resolving (165), not resolved (205) or unknown (1230) at the time of the reporting; there were 65 cases where a fatal outcome was reported. Drug ineffective cases (1649) - Drug ineffective event seriousness: serious (1625), non-serious (21)^e; - Lack of efficacy term was reported: - after the 1st dose in 788 cases - after the 2nd dose in 139 cases - in 722 cases it was unknown after which dose the lack of efficacy occurred. - Latency of lack of efficacy term reported after the first dose was known for 176 cases: - Within 9 days: 2 subjects; - Within 14 and 21 days: 154 subjects; - Within 22 and 50 days: 20 subjects; - Latency of lack of efficacy term reported after the second dose was known for 69 cases: - Within 0 and 7 days: 42 subjects; - Within 8 and 21 days: 22 subjects; - Within 23 and 36 days: 5 subjects. - Latency of lack of efficacy term reported in cases where the number of doses administered was not provided, was known in 409 cases: - Within 0 and 7 days after vaccination: 281 subjects. - Within 8 and 14 days after vaccination: 89 subjects. - Within 15 and 44 days after vaccination: 39 subjects. According to the RSI, individuals may not be fully protected until 7 days after their second dose of vaccine, therefore for the above 1649 cases where lack of efficacy was reported after the 1st dose or the		

Table 6. Description of Missing Information

Topic	Description
Missing Information	Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)
	2nd dose, the reported events may represent signs and symptoms of intercurrent or undiagnosed COVID-19 infection or infection in an individual who was not fully vaccinated, rather than vaccine ineffectiveness. <i>Vaccination failure cases (16)</i> • Vaccination failure seriousness: all serious; • Lack of efficacy term was reported in all cases after the 2nd dose; • Latency of lack of efficacy was known for 14 cases: ○ Within 7 and 13 days: 8 subjects; ○ Within 15 and 29 days: 6 subjects. COVID-19 (10) and Asymptomatic COVID-19 (6) were the reported vaccine preventable infections that occurred in these 16 cases. Conclusion: No new safety signals of vaccine lack of efficacy have emerged based on a review of these cases.

- From a total of 417 cases, 4 cases were excluded from the analysis. In 3 cases, the MAH was informed that a 33-year-old and two unspecified age pregnant female patients were scheduled to receive bnt162b2 (PT reported Off label use and Product use issue in 2 cases; Circumstance or information capable of leading to medication error in one case). One case reported the PT Morning sickness; however, pregnancy was not confirmed in this case.
- 558 additional cases retrieved in this dataset were excluded from the analysis; upon review, 546 cases cannot be considered true lack of efficacy cases because the PT Drug ineffective was coded but the subjects developed SARS-CoV-2 infection during the early days from the first dose (days 1 – 13); the vaccine has not had sufficient time to stimulate the immune system and, consequently, the development of a vaccine preventable disease during this time is not considered a potential lack of effect of the vaccine; in 5 cases the PT Drug ineffective was removed after data lock point (DLP) because the subjects did not develop COVID-19 infection; in 1 case, reporting Treatment failure and Transient ischaemic attack, the Lack of efficacy PT did not refer to BNT162b2 vaccine; 5 cases have been invalidated in the safety database after DLP; 1 case has been deleted from the discussion because the PTs reported Pathogen resistance and Product preparation issue were not indicative of a lack of efficacy. to be eliminated.
- Upon review, 31 additional cases were excluded from the analysis as the data reported (e.g. clinical details, height, weight, etc.) were not consistent with paediatric subjects
- Upon review, 28 additional cases were excluded from the analysis as the data reported (e.g. clinical details, height, weight, etc.) were not consistent with paediatric subjects.
- Different clinical outcomes may be reported for an event that occurred more than once to the same individual
- In 2 cases the PT Vaccination failure was replaced with Drug ineffective after DLP. Another case was not included in the discussion of the Vaccination failure cases because correct scheduling (21 days apart between the first and second dose) cannot be confirmed.

3.1.3. Review of Adverse Events of Special Interest (AESIs)

Please refer to [Appendix 1](#) for the list of the company's AESIs for BNT162b2.

The company's AESI list takes into consideration the lists of AESIs from the following expert groups and regulatory authorities: Brighton Collaboration (SPEAC), ACCESS protocol, US CDC (preliminary list of AESI for VAERS surveillance), MHRA (unpublished guideline).

The AESI terms are incorporated into a TME list and include events of interest due to their association with severe COVID-19 and events of interest for vaccines in general.

The AESI list is comprised of MedDRA PTs, HLTs, HLGs or MedDRA SMQs and can be changed as appropriate based on the evolving safety profile of the vaccine.

Table 7 provides a summary review of cumulative cases within AESI categories in the Pfizer safety database. This is distinct from safety signal evaluations which are conducted and included, as appropriate, in the Summary Monthly Safety Reports submitted regularly to the FDA and other Health Authorities.

Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
Anaphylactic Reactions <i>Search criteria: Anaphylactic reaction SMQ (Narrow and Broad, with the algorithm applied), selecting relevant cases according to BC criteria</i>	Please refer to the Risk 'Anaphylaxis' included above in Table 4 .
Cardiovascular AESIs <i>Search criteria: PTs Acute myocardial infarction; Arrhythmia; Cardiac failure; Cardiac failure acute; Cardiogenic shock; Coronary artery disease; Myocardial infarction; Postural orthostatic tachycardia syndrome; Stress cardiomyopathy; Tachycardia</i>	• Number of cases: 1403 (3.3% of the total PM dataset), of which 241 are medically confirmed and 1162 are non-medically confirmed; • Country of incidence: UK (268), US (233), Mexico (196), Italy (141), France (128), Germany (102), Spain (46), Greece (45), Portugal (37), Sweden (20), Ireland (17), Poland (16), Israel (13), Austria, Romania and Finland (12 each), Netherlands (11), Belgium and Norway (10 each), Czech Republic (9), Hungary and Canada (8 each), Croatia and Denmark (7 each), Iceland (5); the remaining 30 cases were distributed among 13 other countries; • Subjects' gender: female (1076), male (291) and unknown (36); • Subjects' age group (n = 1346): Adult^c (1078), Elderly^d (266) Child^e and Adolescent^f (1 each); • Number of relevant events: 1441, of which 946 serious, 495 non-serious; in the cases reporting relevant serious events; • Reported relevant PTs: Tachycardia (1098), Arrhythmia (102), Myocardial infarction (89), Cardiac failure (80), Acute myocardial infarction (41), Cardiac failure acute (11), Cardiogenic shock and Postural orthostatic tachycardia syndrome (7 each) and Coronary artery disease (6); • Relevant event onset latency (n = 1209): Range from <24 hours to 21 days, median <24 hours;

Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
	Relevant event outcome^g: fatal (136), resolved/resolving (767), resolved with sequelae (21), not resolved (140) and unknown (380); Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue
COVID-19 AESIs <i>Search criteria: Covid-19 SMQ (Narrow and Broad) OR PTs Ageusia; Anosmia</i>	- Number of cases: 3067 (7.3% of the total PM dataset), of which 1013 are medically confirmed and 2054 are non-medically confirmed; - Country of incidence: US (1272), UK (609), Germany (360), France (161), Italy (94), Spain (69), Romania (62), Portugal (51), Poland (50), Mexico (43), Belgium (42), Israel (41), Sweden (30), Austria (27), Greece (24), Denmark (18), Czech Republic and Hungary (17 each), Canada (12), Ireland (11), Slovakia (9), Latvia and United Arab Emirates (6 each); the remaining 36 cases were distributed among 16 other different countries; - Subjects' gender: female (1650), male (844) and unknown (573); - Subjects' age group (n= 1880): Adult (1315), Elderly (560), Infant^h and Adolescent (2 each), Child (1); - Number of relevant events: 3359, of which 2585 serious, 774 non-serious; - Most frequently reported relevant PTs (>1 occurrence): COVID-19 (1927), SARS-CoV-2 test positive (415), Suspected COVID-19 (270), Ageusia (228), Anosmia (194), SARS-CoV-2 antibody test negative (83), Exposure to SARS-CoV-2 (62), SARS-CoV-2 antibody test positive (53), COVID-19 pneumonia (51), Asymptomatic COVID-19 (31), Coronavirus infection (13), Occupational exposure to SARS-CoV-2 (11), SARS-CoV-2 test false positive (7), Coronavirus test positive (6), SARS-CoV-2 test negative (3) SARS-CoV-2 antibody test (2); - Relevant event onset latency (n = 2070): Range from <24 hours to 374 days, median 5 days; - Relevant event outcome: fatal (136), not resolved (547), resolved/resolving (558), resolved with sequelae (9) and unknown (2110). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue
Dermatological AESIs <i>Search criteria: PT Chillblains; Erythema multiforme</i>	- Number of cases: 20 cases (0.05% of the total PM dataset), of which 15 are medically confirmed and 5 are non-medically confirmed; - Country of incidence: UK (8), France and Poland (2 each), and the remaining 8 cases were distributed among 8 other different countries; - Subjects' gender: female (17) male and unknown (1 each); - Subjects' age group (n=19): Adult (18), Elderly (1); - Number of relevant events: 20 events, 16 serious, 4 non-serious

Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
	- Reported relevant PTs: Erythema multiforme (13) and Chillblains (7) - Relevant event onset latency (n = 18): Range from <24 hours to 17 days, median 3 days; - Relevant event outcome: resolved/resolving (7), not resolved (8) and unknown (6). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.
Haematological AESIs <i>Search criteria: Leukopenias NEC (HLT) (Primary Path) OR Neutropenias (HLT) (Primary Path) OR PTs Immune thrombocytopenia, Thrombocytopenia OR SMQ Haemorrhage terms (excl laboratory terms)</i>	- Number of cases: 932 (2.2 % of the total PM dataset), of which 524 medically confirmed and 408 non-medically confirmed; - Country of incidence: UK (343), US (308), France (50), Germany (43), Italy (37), Spain (27), Mexico and Poland (13 each), Sweden (10), Israel (9), Netherlands (8), Denmark, Finland, Portugal and Ireland (7 each), Austria and Norway (6 each), Croatia (4), Greece, Belgium, Hungary and Switzerland (3 each), Cyprus, Latvia and Serbia (2 each); the remaining 9 cases originated from 9 different countries; - Subjects' gender (n=898): female (676) and male (222); - Subjects' age group (n=837): Adult (543), Elderly (293), Infant (1); - Number of relevant events: 1080, of which 681 serious, 399 non-serious; - Most frequently reported relevant PTs (≥15 occurrences) include: Epistaxis (127), Contusion (112), Vaccination site bruising (96), Vaccination site haemorrhage (51), Petechiae (50), Haemorrhage (42), Haematochezia (34), Thrombocytopenia (33), Vaccination site hematoma (32), Conjunctival haemorrhage and Vaginal haemorrhage (29 each), Haematoma, Haemoptysis and Menorrhagia (27 each), Haematemesis (25), Eye haemorrhage (23), Rectal haemorrhage (22), Immune thrombocytopenia (20), Blood urine present (19), Haematuria, Neutropenia and Purpura (16 each) Diarrhoea haemorrhagic (15); - Relevant event onset latency (n = 787): Range from <24 hours to 33 days, median = 1 day; - Relevant event outcome: fatal (34), resolved/resolving (393), resolved with sequelae (17), not resolved (267) and unknown (371). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue
Hepatic AESIs <i>Search criteria: Liver related investigations, signs and symptoms (SMQ) (Narrow and Broad) OR PT Liver injury</i>	- Number of cases: 70 cases (0.2% of the total PM dataset), of which 54 medically confirmed and 16 non-medically confirmed; - Country of incidence: UK (19), US (14), France (7), Italy (5), Germany (4), Belgium, Mexico and Spain (3 each), Austria, and Iceland (2 each); the remaining 8 cases originated from 8 different countries; - Subjects' gender: female (43), male (26) and unknown (1); - Subjects' age group (n=64): Adult (37), Elderly (27);

Table 7. AESIs Evaluation for BNT162b2

AESIs ^a Category	Post-Marketing Cases Evaluation ^b Total Number of Cases (N=42086)
	• Number of relevant events: 94, of which 53 serious, 41 non-serious; • Most frequently reported relevant PTs (≥ 3 occurrences) include: Alanine aminotransferase increased (16), Transaminases increased and Hepatic pain (9 each), Liver function test increased (8), Aspartate aminotransferase increased and Liver function test abnormal (7 each), Gamma-glutamyltransferase increased and Hepatic enzyme increased (6 each), Blood alkaline phosphatase increased and Liver injury (5 each), Ascites, Blood bilirubin increased and Hypertransaminasaemia (3 each); • Relevant event onset latency (n = 57): Range from <24 hours to 20 days, median 3 days; • Relevant event outcome: fatal (5), resolved/resolving (27), resolved with sequelae (1), not resolved (14) and unknown (47). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue
Facial Paralysis <i>Search criteria: PTs Facial paralysis, Facial paresis</i>	• Number of cases: 449ⁱ (1.07% of the total PM dataset), 314 medically confirmed and 135 non-medically confirmed; • Country of incidence: US (124), UK (119), Italy (40), France (27), Israel (20), Spain (18), Germany (13), Sweden (11), Ireland (9), Cyprus (8), Austria (7), Finland and Portugal (6 each), Hungary and Romania (5 each), Croatia and Mexico (4 each), Canada (3), Czech Republic, Malta, Netherlands, Norway, Poland and Puerto Rico (2 each); the remaining 8 cases originated from 8 different countries; • Subjects' gender: female (295), male (133), unknown (21); • Subjects' age group (n=411): Adult (313), Elderly (96), Infant^j and Child (1 each); • Number of relevant events^k: 453, of which 399 serious, 54 non-serious; • Reported relevant PTs: Facial paralysis (401), Facial paresis (64); • Relevant event onset latency (n = 404): Range from <24 hours to 46 days, median 2 days; • Relevant event outcome: resolved/resolving (184), resolved with sequelae (3), not resolved (183) and unknown (97); Overall Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue. Causality assessment will be further evaluated following availability of additional unblinded data from the clinical study C4591001, which will be unblinded for final analysis approximately mid-April 2021. Additionally, non-interventional post-authorisation safety studies, C4591011 and C4591012 are expected to capture data on a sufficiently large vaccinated population to detect an increased risk of Bell's palsy in vaccinated individuals. The timeline for conducting these analyses will be established based on the size of the vaccinated population captured in the study data sources by the first interim reports (due 30 June

Table 7. AESIs Evaluation for BNT162b2

AESIs ^a Category	Post-Marketing Cases Evaluation ^b Total Number of Cases (N=42086)
Immune-Mediated/Autoimmune AESIs <i>Search criteria: Immune-mediated/autoimmune disorders (SMQ) (Broad and Narrow) OR Autoimmune disorders HLGT (Primary Path) OR PTs Cytokine release syndrome; Cytokine storm; Hypersensitivity</i>	2021). Study C4591021, pending protocol endorsement by EMA, is also intended to inform this risk. - Number of cases: 1050 (2.5 % of the total PM dataset), of which 760 medically confirmed and 290 non-medically confirmed; - Country of incidence (>10 cases): UK (267), US (257), Italy (70), France and Germany (69 each), Mexico (36), Sweden (35), Spain (32), Greece (31), Israel (21), Denmark (18), Portugal (17), Austria and Czech Republic (16 each), Canada (12), Finland (10). The remaining 74 cases were from 24 different countries. - Subjects' gender (n=682): female (526), male (156). - Subjects' age group (n=944): Adult (746), Elderly (196), Adolescent (2). - Number of relevant events: 1077, of which 780 serious, 297 non-serious. - Most frequently reported relevant PTs (>10 occurrences): Hypersensitivity (596), Neuropathy peripheral (49), Pericarditis (32), Myocarditis (25), Dermatitis (24), Diabetes mellitus and Encephalitis (16 each), Psoriasis (14), Dermatitis Bullous (13), Autoimmune disorder and Raynaud's phenomenon (11 each); - Relevant event onset latency (n = 807): Range from <24 hours to 30 days, median <24 hours. - Relevant event outcome¹: resolved/resolving (517), not resolved (215), fatal (12), resolved with sequelae (22) and unknown (312). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue
Musculoskeletal AESIs <i>Search criteria: PTs Arthralgia; Arthritis; Arthritis bacterial¹; Chronic fatigue syndrome; Polyarthrititis; Polyneuropathy; Post viral fatigue syndrome; Rheumatoid arthritis</i>	- Number of cases: 3600 (8.5% of the total PM dataset), of which 2045 medically confirmed and 1555 non-medically confirmed; - Country of incidence: UK (1406), US (1004), Italy (285), Mexico (236), Germany (72), Portugal (70), France (48), Greece and Poland (46), Latvia (33), Czech Republic (32), Israel and Spain (26), Sweden (25), Romania (24), Denmark (23), Finland and Ireland (19 each), Austria and Belgium (18 each), Canada (16), Netherlands (14), Bulgaria (12), Croatia and Serbia (9 each), Cyprus and Hungary (8 each), Norway (7), Estonia and Puerto Rico (6 each), Iceland and Lithuania (4 each); the remaining 21 cases originated from 11 different countries; - Subjects' gender (n=3471): female (2760), male (711); - Subjects' age group (n=3372): Adult (2850), Elderly (515), Child (4), Adolescent (2), Infant (1); - Number of relevant events: 3640, of which 1614 serious, 2026 non-serious; - Reported relevant PTs: Arthralgia (3525), Arthritis (70), Rheumatoid arthritis (26), Polyarthrititis (5), Polyneuropathy, Post viral fatigue syndrome, Chronic fatigue syndrome (4 each), Arthritis bacterial (1); - Relevant event onset latency (n = 2968): Range from <24 hours to 32 days, median 1 day;

Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
	Relevant event outcome: resolved/resolving (1801), not resolved (959), resolved with sequelae (49), and unknown (853). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.
Neurological AESIs (including demyelination) <i>Search criteria: Convulsions (SMQ) (Broad and Narrow) OR Demyelination (SMQ) (Broad and Narrow) OR PTs Ataxia; Cataplexy; Encephalopathy; Fibromyalgia; Intracranial pressure increased; Meningitis; Meningitis aseptic; Narcolepsy</i>	- Number of cases: 501 (1.2% of the total PM dataset), of which 365 medically confirmed and 136 non-medically confirmed. - Country of incidence (≥ 9 cases): UK (157), US (68), Germany (49), Mexico (35), Italy (31), France (25), Spain (18), Poland (17), Netherlands and Israel (15 each), Sweden (9). The remaining 71 cases were from 22 different countries. - Subjects' gender (n=478): female (328), male (150). - Subjects' age group (n=478): Adult (329), Elderly (149); - Number of relevant events: 542, of which 515 serious, 27 non-serious. - Most frequently reported relevant PTs (>2 occurrences) included: Seizure (204), Epilepsy (83), Generalised tonic-clonic seizure (33), Guillain-Barre syndrome (24), Fibromyalgia and Trigeminal neuralgia (17 each), Febrile convulsion, (15), Status epilepticus (12), Aura and Myelitis transverse (11 each), Multiple sclerosis relapse and Optic neuritis (10 each), Petit mal epilepsy and Tonic convulsion (9 each), Ataxia (8), Encephalopathy and Tonic clonic movements (7 each), Foaming at mouth (5), Multiple sclerosis, Narcolepsy and Partial seizures (4 each), Bad sensation, Demyelination, Meningitis, Postictal state, Seizure like phenomena and Tongue biting (3 each); - Relevant event onset latency (n = 423): Range from <24 hours to 48 days, median 1 day; - Relevant events outcome: fatal (16), resolved/resolving (265), resolved with sequelae (13), not resolved (89) and unknown (161); Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue
Other AESIs <i>Search criteria: Herpes viral infections (HLT) (Primary Path) OR PTs Adverse event following immunisation; Inflammation; Manufacturing laboratory analytical testing issue; Manufacturing materials issue; Manufacturing production issue; MERS-CoV test; MERS-CoV test negative; MERS-CoV test positive; Middle East respiratory syndrome; Multiple organ dysfunction syndrome; Occupational exposure to communicable disease; Patient</i>	- Number of cases: 8152 (19.4% of the total PM dataset), of which 4977 were medically confirmed and 3175 non-medically confirmed; - Country of incidence (> 20 occurrences): UK (2715), US (2421), Italy (710), Mexico (223), Portugal (210), Germany (207), France (186), Spain (183), Sweden (133), Denmark (127), Poland (120), Greece (95), Israel (79), Czech Republic (76), Romania (57), Hungary (53), Finland (52), Norway (51), Latvia (49), Austria (47), Croatia (42), Belgium (41), Canada (39), Ireland (34), Serbia (28), Iceland (25), Netherlands (22). The remaining 127 cases were from 21 different countries; - Subjects' gender (n=7829): female (5969), male (1860); - Subjects' age group (n=7479): Adult (6330), Elderly (1125), Adolescent, Child (9 each), Infant (6);

Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
<i>isolation; Product availability issue; Product distribution issue; Product supply issue; Pyrexia; Quarantine; SARS-CoV-1 test; SARS-CoV-1 test negative; SARS-CoV-1 test positive</i>	• Number of relevant events: 8241, of which 3674 serious, 4568 non-serious; • Most frequently reported relevant PTs (≥ 6 occurrences) included: Pyrexia (7666), Herpes zoster (259), Inflammation (132), Oral herpes (80), Multiple organ dysfunction syndrome (18), Herpes virus infection (17), Herpes simplex (13), Ophthalmic herpes zoster (10), Herpes ophthalmic and Herpes zoster reactivation (6 each); • Relevant event onset latency (n =6836): Range from <24 hours to 61 days, median 1 day; • Relevant events outcome: fatal (96), resolved/resolving (5008), resolved with sequelae (84), not resolved (1429) and unknown (1685). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue
Pregnancy Related AESIs <i>Search criteria: PTs Amniotic cavity infection; Caesarean section; Congenital anomaly; Death neonatal; Eclampsia; Foetal distress syndrome; Low birth weight baby; Maternal exposure during pregnancy; Placenta praevia; Pre-eclampsia; Premature labour; Stillbirth; Uterine rupture; Vasa praevia</i>	For relevant cases, please refer to Table 6, Description of Missing Information, Use in Pregnancy and While Breast Feeding
Renal AESIs <i>Search criteria: PTs Acute kidney injury; Renal failure.</i>	• Number of cases: 69 cases (0.17% of the total PM dataset), of which 57 medically confirmed, 12 non-medically confirmed; • Country of incidence: Germany (17), France and UK (13 each), US (6), Belgium, Italy and Spain (4 each), Sweden (2), Austria, Canada, Denmark, Finland, Luxembourg and Norway (1 each); • Subjects' gender: female (46), male (23); • Subjects' age group (n=68): Adult (7), Elderly (60), Infant (1); • Number of relevant events: 70, all serious; • Reported relevant PTs: Acute kidney injury (40) and Renal failure (30); • Relevant event onset latency (n = 42): Range from <24 hours to 15 days, median 4 days; • Relevant event outcome: fatal (23), resolved/resolving (10), not resolved (15) and unknown (22). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.
Respiratory AESIs <i>Search criteria: Lower respiratory tract infections NEC (HLT)</i>	• Number of cases: 130 cases (0.3% of the total PM dataset), of which 107 medically confirmed;

Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
<i>(Primary Path) OR Respiratory failures (excl neonatal) (HLT)</i> <i>(Primary Path) OR Viral lower respiratory tract infections (HLT)</i> <i>(Primary Path) OR PTs: Acute respiratory distress syndrome; Endotracheal intubation; Hypoxia; Pulmonary haemorrhage; Respiratory disorder; Severe acute respiratory syndrome</i>	• Countries of incidence: United Kingdom (20), France (18), United States (16), Germany (14), Spain (13), Belgium and Italy (9), Denmark (8), Norway (5), Czech Republic, Iceland (3 each); the remaining 12 cases originated from 8 different countries. • Subjects' gender (n=130): female (72), male (58). • Subjects's age group (n=126): Elderly (78), Adult (47), Adolescent (1). • Number of relevant events: 137, of which 126 serious, 11 non-serious; • Reported relevant PTs: Respiratory failure (44), Hypoxia (42), Respiratory disorder (36), Acute respiratory distress syndrome (10), Chronic respiratory syndrome (3), Severe acute respiratory syndrome (2). • Relevant event onset latency (n=102): range from < 24 hours to 18 days, median 1 day; • Relevant events outcome: fatal (41), Resolved/resolving (47), not recovered (18) and unknown (31). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.
Thromboembolic Events <i>Search criteria: Embolism and thrombosis (HLGT) (Primary Path), excluding PTs reviewed as Stroke AESIs, OR PTs Deep vein thrombosis; Disseminated intravascular coagulation; Embolism; Embolism venous; Pulmonary embolism</i>	• Number of cases: 151 (0.3% of the total PM dataset), of which 111 medically confirmed and 40 non-medically confirmed; • Country of incidence: UK (34), US (31), France (20), Germany (15), Italy and Spain (6 each), Denmark and Sweden (5 each), Austria, Belgium and Israel (3 each), Canada, Cyprus, Netherlands and Portugal (2 each); the remaining 12 cases originated from 12 different countries; • Subjects' gender (n= 144): female (89), male (55); • Subjects' age group (n=136): Adult (66), Elderly (70); • Number of relevant events: 168, of which 165 serious, 3 non-serious; • Most frequently reported relevant PTs (>1 occurrence) included: Pulmonary embolism (60), Thrombosis (39), Deep vein thrombosis (35), Thrombophlebitis superficial (6), Venous thrombosis limb (4), Embolism, Microembolism, Thrombophlebitis and Venous thrombosis (3 each) Blue toe syndrome (2); • Relevant event onset latency (n = 124): Range from <24 hours to 28 days, median 4 days; • Relevant event outcome: fatal (18), resolved/resolving (54), resolved with sequelae (6), not resolved (49) and unknown (42). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.
Stroke <i>Search criteria: HLT Central nervous system haemorrhages and cerebrovascular accidents</i>	• Number of cases: 275 (0.6% of the total PM dataset), of which 180 medically confirmed and 95 non-medically confirmed; • Country of incidence: UK (81), US (66), France (32), Germany (21), Norway (14), Netherlands and Spain (11 each), Sweden (9),

Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
<i>(Primary Path) OR HLT</i> <i>Cerebrovascular venous and sinus thrombosis (Primary Path)</i>	Israel (6), Italy (5), Belgium (3), Denmark, Finland, Poland and Switzerland (2 each); the remaining 8 cases originated from 8 different countries; - Subjects' gender (n= 273): female (182), male (91); - Subjects' age group (n=265): Adult (59), Elderly (205), Child^m (1); - Number of relevant events: 300, all serious; - Most frequently reported relevant PTs (>1 occurrence) included: - PTs indicative of Ischaemic stroke: Cerebrovascular accident (160), Ischaemic stroke (41), Cerebral infarction (15), Cerebral ischaemia, Cerebral thrombosis, Cerebral venous sinus thrombosis, Ischaemic cerebral infarction and Lacunal infarction (3 each) Basal ganglia stroke, Cerebellar infarction and Thrombotic stroke (2 each); - PTs indicative of Haemorrhagic stroke: Cerebral haemorrhage (26), Haemorrhagic stroke (11), Haemorrhage intracranial and Subarachnoid haemorrhage (5 each), Cerebral haematoma (4), Basal ganglia haemorrhage and Cerebellar haemorrhage (2 each); - Relevant event onset latency (n = 241): Range from <24 hours to 41 days, median 2 days; - Relevant event outcome: fatal and resolved/resolving (61 each), resolved with sequelae (10), not resolved (85) and unknown (83). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.
Vasculitic Events <i>Search criteria: Vasculitides HLT</i>	- Number of cases: 32 cases (0.08% of the total PM dataset), of which 26 medically confirmed and 6 non-medically confirmed; - Country of incidence: UK (13), France (4), Portugal, US and Spain (3 each), Cyprus, Germany, Hungary, Italy and Slovakia and Costa Rica (1 each); - Subjects' gender: female (26), male (6); - Subjects' age group (n=31): Adult (15), Elderly (16); - Number of relevant events: 34, of which 25 serious, 9 non-serious; - Reported relevant PTs: Vasculitis (14), Cutaneous vasculitis and Vasculitic rash (4 each), (3), Giant cell arteritis and Peripheral ischaemia (3 each), Behcet's syndrome and Hypersensitivity vasculitis (2 each) Palpable purpura, and Takayasu's arteritis (1 each); - Relevant event onset latency (n = 25): Range from <24 hours to 19 days, median 3 days; - Relevant event outcome: fatal (1), resolved/resolving (13), not resolved (12) and unknown (8). Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue

Table 7. AESIs Evaluation for BNT162b2

AESIs ^a Category	Post-Marketing Cases Evaluation ^b Total Number of Cases (N=42086)
--------------------------------	---

- a. For the complete list of the AESIs, please refer to Appendix 5;
- b. Please note that this corresponds to evidence from post-EUA/conditional marketing authorisation approval data sources;
- c. Subjects with age ranged between 18 and 64 years;
- d. Subjects with age equal to or above 65 years;
- e. Subjects with age ranged between 2 and 11 years;
- f. Subjects with age ranged between 12 and less than 18 years;
- g. Multiple episodes of the same PT event were reported with a different clinical outcome within some cases hence the sum of the events outcome exceeds the total number of PT events;
- h. Subjects with age ranged between 1 (28 days) and 23 months;
- i. Twenty-four additional cases were excluded from the analysis as they were not cases of peripheral facial nerve palsy because they described other disorders (stroke, cerebral haemorrhage or transient ischaemic attack); 1 case was excluded from the analysis because it was invalid due to an unidentifiable reporter;
- j. This UK case report received from the UK MHRA described a 1-year-old subject who received the vaccine, and had left postauricular ear pain that progressed to left-sided Bell's palsy 1 day following vaccination that had not resolved at the time of the report;
- k. If a case included both PT Facial paresis and PT Facial paralysis, only the PT Facial paralysis was considered in the descriptions of the events as it is most clinically important;
- l. Multiple episodes of the same PT event were reported with a different clinical outcome within some cases hence the sum of the events outcome exceeds the total number of PT events
- m. This UK case report received from the UK MHRA described a 7-year-old female subject who received the vaccine and had stroke (unknown outcome); no follow-up is possible for clarification.
- n. This PT not included in the AESIs/TME list was included in the review as relevant for ACCESS protocol criteria;

3.1.4. Medication error

Cases potentially indicative of medication errors¹ that cumulatively occurred are summarized below.

- Number of relevant medication error cases: 2056² (4.9%) of which 1569 (3.7%) are medically confirmed.
- Number of relevant events: 2792
- Top 10 countries of incidence:
 - US (1201), France (171), UK (138), Germany (88), Czech Republic (87), Sweden (49), Israel (45), Italy (42), Canada (35), Romania (33), Finland (21), Portugal (20), Norway (14), Puerto Rico (13), Poland (12), Austria and Spain (10 each).

Medication error case outcomes:

- Fatal (7)³,
- Recovered/recovering (354, of which 4 are serious),
- Recovered with sequelae (8, of which 3 serious)

¹ MedDRA (version 23.1) Higher Level Terms: Accidental exposures to product; Product administration errors and issues; Product confusion errors and issues; Product dispensing errors and issues; Product label issues; Product monitoring errors and issues; Product preparation errors and issues; Product selection errors and issues; Product storage errors and issues in the product use system; Product transcribing errors and communication issues, OR Preferred Terms: Accidental poisoning; Circumstance or information capable of leading to device use error; Circumstance or information capable of leading to medication error; Contraindicated device used; Deprescribing error; Device use error; Dose calculation error; Drug titration error; Expired device used; Exposure via direct contact; Exposure via eye contact; Exposure via mucosa; Exposure via skin contact; Failure of child resistant product closure; Inadequate aseptic technique in use of product; Incorrect disposal of product; Intercepted medication error; Intercepted product prescribing error; Medication error; Multiple use of single-use product; Product advertising issue; Product distribution issue; Product prescribing error; Product prescribing issue; Product substitution error; Product temperature excursion issue; Product use in unapproved therapeutic environment; Radiation underdose; Underdose; Unintentional medical device removal; Unintentional use for unapproved indication; Vaccination error; Wrong device used; Wrong dosage form; Wrong dosage formulation; Wrong dose; Wrong drug; Wrong patient; Wrong product procured; Wrong product stored; Wrong rate; Wrong route; Wrong schedule; Wrong strength; Wrong technique in device usage process; Wrong technique in product usage process.

² Thirty-five (35) cases were excluded from the analysis because describing medication errors occurring in an unspecified number of individuals or describing medication errors occurring with co suspects were determined to be non-contributory.

³ All the medication errors reported in these cases were assessed as non-serious occurrences with an unknown outcome; based on the available information including the causes of death, the relationship between the medication error and the death is weak. .

- Not recovered (189, of which 84 are serious),
- Unknown (1498, of which 33 are serious).

1371 cases reported only MEs without any associated clinical adverse event. The PTs most frequently reported (≥ 12 occurrences) were: Poor quality product administered (539), Product temperature excursion issue (253), Inappropriate schedule of product administration (225), Product preparation error (206), Underdose (202), Circumstance or information capable of leading to medication error (120), Product preparation issue (119), Wrong technique in product usage process (76), Incorrect route of product administration (66), Accidental overdose (33), Product administered at inappropriate site (27), Incorrect dose administered and Accidental exposure to the product (25 each), Exposure via skin contact (22), Wrong product administered (17), Incomplete course of vaccination, and Product administration error (14 each) Product administered to patient of inappropriate age (12).

In 685 cases, there were co-reported AEs. The most frequently co-associated AEs (> 40 occurrences) were: Headache (187), Pyrexia (161), Fatigue (135), Chills (127), Pain (107), Vaccination site pain (100), Nausea (89), Myalgia (88), Pain in extremity (85) Arthralgia (68), Off label use (57), Dizziness (52), Lymphadenopathy (47), Asthenia (46) and Malaise (41). These cases are summarized in Table 8.

Table 8. ME PTs by seriousness with or without harm co-association (Through 28 February 2021)

ME PTs	Serious		Non-Serious	
	With Harm	Without Harm	With Harm	Without Harm
Accidental exposure to product	0	0	0	5
Accidental overdose	4	1	9	6
Booster dose missed	0	0	0	1
Circumstance or information capable of leading to medication error	0	0	5	11
Contraindicated product administered	1	0	0	2
Expired product administered	0	0	0	2
Exposure via skin contact	0	0	0	5
Inappropriate schedule of product administration	0	2	8	264
Incorrect dose administered	1	1	0	0

Table 8. ME PTs by seriousness with or without harm co-association (Through 28 February 2021)

ME PTs	Serious		Non-Serious	
	With Harm	Without Harm	With Harm	Without Harm
Incorrect route of product administration	2	6	16	127
Lack of vaccination site rotation	1	0	0	0
Medication error	0	0	0	1
Poor quality product administered	1	0	0	34
Product administered at inappropriate site	2	1	13	29
Product administered to patient of inappropriate age	0	4	0	40
Product administration error	1	0	0	3
Product dose omission issue	0	1	0	3
Product preparation error	1	0	4	11
Product preparation issue	1	1	0	14

Overall, there were 68 cases with co-reported AEs reporting Harm and 599 cases with co-reported AEs without harm. Additionally, Intercepted medication errors was reported in 1 case (PTs Malaise, clinical outcome unknow) and Potential medication errors were reported in 17 cases.

4. DISCUSSION

Pfizer performs frequent and rigorous signal detection on BNT162b2 cases. The findings of these signal detection analyses are consistent with the known safety profile of the vaccine. This cumulative analysis to support the Biologics License Application for BNT162b2, is an integrated analysis of post-authorization safety data, from U.S. and foreign experience, focused on Important Identified Risks, Important Potential Risks, and areas of Important Missing Information identified in the Pharmacovigilance Plan, as well as adverse events of special interest and vaccine administration errors (whether or not associated with an adverse event). The data do not reveal any novel safety concerns or risks requiring label changes and support a favorable benefit risk profile of to the BNT162b2 vaccine.

5. SUMMARY AND CONCLUSION

Review of the available data for this cumulative PM experience, confirms a favorable benefit: risk balance for BNT162b2.

Pfizer will continue routine pharmacovigilance activities on behalf of BioNTech according to the Pharmacovigilance Agreement in place, in order to assure patient safety and will inform the Agency if an evaluation of the safety data yields significant new information for BNT162b2.

APPENDIX 1. LIST OF ADVERSE EVENTS OF SPECIAL INTEREST

1p36 deletion syndrome; 2-Hydroxyglutaric aciduria; 5'nucleotidase increased; Acoustic neuritis; Acquired C1 inhibitor deficiency; Acquired epidermolysis bullosa; Acquired epileptic aphasia; Acute cutaneous lupus erythematosus; Acute disseminated encephalomyelitis; Acute encephalitis with refractory, repetitive partial seizures; Acute febrile neutrophilic dermatosis; Acute flaccid myelitis; Acute haemorrhagic leukoencephalitis; Acute haemorrhagic oedema of infancy; Acute kidney injury; Acute macular outer retinopathy; Acute motor axonal neuropathy; Acute motor-sensory axonal neuropathy; Acute myocardial infarction; Acute respiratory distress syndrome; Acute respiratory failure; Addison's disease; Administration site thrombosis; Administration site vasculitis; Adrenal thrombosis; Adverse event following immunisation; Ageusia; Agranulocytosis; Air embolism; Alanine aminotransferase abnormal; Alanine aminotransferase increased; Alcoholic seizure; Allergic bronchopulmonary mycosis; Allergic oedema; Alloimmune hepatitis; Alopecia areata; Alpers disease; Alveolar proteinosis; Ammonia abnormal; Ammonia increased; Amniotic cavity infection; Amygdalohippocampectomy; Amyloid arthropathy; Amyloidosis; Amyloidosis senile; Anaphylactic reaction; Anaphylactic shock; Anaphylactic transfusion reaction; Anaphylactoid reaction; Anaphylactoid shock; Anaphylactoid syndrome of pregnancy; Angioedema; Angiopathic neuropathy; Ankylosing spondylitis; Anosmia; Antiacetylcholine receptor antibody positive; Anti-actin antibody positive; Anti-aquaporin-4 antibody positive; Anti-basal ganglia antibody positive; Anti-cyclic citrullinated peptide antibody positive; Anti-epithelial antibody positive; Anti-erythrocyte antibody positive; Anti-exosome complex antibody positive; Anti-GAD antibody negative; Anti-GAD antibody positive; Anti-ganglioside antibody positive; Antigliadin antibody positive; Anti-glomerular basement membrane antibody positive; Anti-glomerular basement membrane disease; Anti-glycyl-tRNA synthetase antibody positive; Anti-HLA antibody test positive; Anti-IA2 antibody positive; Anti-insulin antibody increased; Anti-insulin antibody positive; Anti-insulin receptor antibody increased; Anti-insulin receptor antibody positive; Anti-interferon antibody negative; Anti-interferon antibody positive; Anti-islet cell antibody positive; Antimitochondrial antibody positive; Anti-muscle specific kinase antibody positive; Anti-myelin-associated glycoprotein antibodies positive; Anti-myelin-associated glycoprotein associated polyneuropathy; Antimyocardial antibody positive; Anti-neuronal antibody positive; Antineutrophil cytoplasmic antibody increased; Antineutrophil cytoplasmic antibody positive; Anti-neutrophil cytoplasmic antibody positive vasculitis; Anti-NMDA antibody positive; Antinuclear antibody increased; Antinuclear antibody positive; Antiphospholipid antibodies positive; Antiphospholipid syndrome; Anti-platelet antibody positive; Anti-prothrombin antibody positive; Antiribosomal P antibody positive; Anti-RNA polymerase III antibody positive; Anti-saccharomyces cerevisiae antibody test positive; Anti-sperm antibody positive; Anti-SRP antibody positive; Antisynthetase syndrome; Anti-thyroid antibody positive; Anti-transglutaminase antibody increased; Anti-VGCC antibody positive; Anti-VGKC antibody positive; Anti-vimentin antibody positive; Antiviral prophylaxis; Antiviral treatment; Anti-zinc transporter 8 antibody positive; Aortic embolus; Aortic thrombosis; Aortitis; Aplasia pure red cell; Aplastic anaemia; Application site thrombosis; Application site vasculitis; Arrhythmia; Arterial bypass occlusion; Arterial bypass thrombosis; Arterial thrombosis; Arteriovenous fistula thrombosis; Arteriovenous graft site stenosis; Arteriovenous graft thrombosis; Arteritis; Arteritis

coronary; Arthralgia; Arthritis; Arthritis enteropathic; Ascites; Aseptic cavernous sinus thrombosis; Aspartate aminotransferase abnormal; Aspartate aminotransferase increased; Aspartate-glutamate-transporter deficiency; AST to platelet ratio index increased; AST/ALT ratio abnormal; Asthma; Asymptomatic COVID-19; Ataxia; Atheroembolism; Atonic seizures; Atrial thrombosis; Atrophic thyroiditis; Atypical benign partial epilepsy; Atypical pneumonia; Aura; Autoantibody positive; Autoimmune anaemia; Autoimmune aplastic anaemia; Autoimmune arthritis; Autoimmune blistering disease; Autoimmune cholangitis; Autoimmune colitis; Autoimmune demyelinating disease; Autoimmune dermatitis; Autoimmune disorder; Autoimmune encephalopathy; Autoimmune endocrine disorder; Autoimmune enteropathy; Autoimmune eye disorder; Autoimmune haemolytic anaemia; Autoimmune heparin-induced thrombocytopenia; Autoimmune hepatitis; Autoimmune hyperlipidaemia; Autoimmune hypothyroidism; Autoimmune inner ear disease; Autoimmune lung disease; Autoimmune lymphoproliferative syndrome; Autoimmune myocarditis; Autoimmune myositis; Autoimmune nephritis; Autoimmune neuropathy; Autoimmune neutropenia; Autoimmune pancreatitis; Autoimmune pancytopenia; Autoimmune pericarditis; Autoimmune retinopathy; Autoimmune thyroid disorder; Autoimmune thyroiditis; Autoimmune uveitis; Autoinflammation with infantile enterocolitis; Autoinflammatory disease; Automatism epileptic; Autonomic nervous system imbalance; Autonomic seizure; Axial spondyloarthritis; Axillary vein thrombosis; Axonal and demyelinating polyneuropathy; Axonal neuropathy; Bacterascites; Baltic myoclonic epilepsy; Band sensation; Basedow's disease; Basilar artery thrombosis; Basophilopenia; B-cell aplasia; Behcet's syndrome; Benign ethnic neutropenia; Benign familial neonatal convulsions; Benign familial pemphigus; Benign rolandic epilepsy; Beta-2 glycoprotein antibody positive; Bickerstaff's encephalitis; Bile output abnormal; Bile output decreased; Biliary ascites; Bilirubin conjugated abnormal; Bilirubin conjugated increased; Bilirubin urine present; Biopsy liver abnormal; Biotinidase deficiency; Birdshot chorioretinopathy; Blood alkaline phosphatase abnormal; Blood alkaline phosphatase increased; Blood bilirubin abnormal; Blood bilirubin increased; Blood bilirubin unconjugated increased; Blood cholinesterase abnormal; Blood cholinesterase decreased; Blood pressure decreased; Blood pressure diastolic decreased; Blood pressure systolic decreased; Blue toe syndrome; Brachiocephalic vein thrombosis; Brain stem embolism; Brain stem thrombosis; Bromosulphthalein test abnormal; Bronchial oedema; Bronchitis; Bronchitis mycoplasmal; Bronchitis viral; Bronchopulmonary aspergillosis allergic; Bronchospasm; Budd-Chiari syndrome; Bulbar palsy; Butterfly rash; C1q nephropathy; Caesarean section; Calcium embolism; Capillaritis; Caplan's syndrome; Cardiac amyloidosis; Cardiac arrest; Cardiac failure; Cardiac failure acute; Cardiac sarcoidosis; Cardiac ventricular thrombosis; Cardiogenic shock; Cardiolipin antibody positive; Cardiopulmonary failure; Cardio-respiratory arrest; Cardio-respiratory distress; Cardiovascular insufficiency; Carotid arterial embolus; Carotid artery thrombosis; Cataplexy; Catheter site thrombosis; Catheter site vasculitis; Cavernous sinus thrombosis; CDKL5 deficiency disorder; CEC syndrome; Cement embolism; Central nervous system lupus; Central nervous system vasculitis; Cerebellar artery thrombosis; Cerebellar embolism; Cerebral amyloid angiopathy; Cerebral arteritis; Cerebral artery embolism; Cerebral artery thrombosis; Cerebral gas embolism; Cerebral microembolism; Cerebral septic infarct; Cerebral thrombosis; Cerebral venous sinus thrombosis; Cerebral venous thrombosis; Cerebrospinal thrombotic

tamponade;Cerebrovascular accident;Change in seizure presentation;Chest discomfort;Child-Pugh-Turcotte score abnormal;Child-Pugh-Turcotte score increased;Chillblains;Choking;Choking sensation;Cholangitis sclerosing;Chronic autoimmune glomerulonephritis;Chronic cutaneous lupus erythematosus;Chronic fatigue syndrome;Chronic gastritis;Chronic inflammatory demyelinating polyradiculoneuropathy;Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids;Chronic recurrent multifocal osteomyelitis;Chronic respiratory failure;Chronic spontaneous urticaria;Circulatory collapse;Circumoral oedema;Circumoral swelling;Clinically isolated syndrome;Clonic convulsion;Coeliac disease;Cogan's syndrome;Cold agglutinins positive;Cold type haemolytic anaemia;Colitis;Colitis erosive;Colitis herpes;Colitis microscopic;Colitis ulcerative;Collagen disorder;Collagen-vascular disease;Complement factor abnormal;Complement factor C1 decreased;Complement factor C2 decreased;Complement factor C3 decreased;Complement factor C4 decreased;Complement factor decreased;Computerised tomogram liver abnormal;Concentric sclerosis;Congenital anomaly;Congenital bilateral perisylvian syndrome;Congenital herpes simplex infection;Congenital myasthenic syndrome;Congenital varicella infection;Congestive hepatopathy;Convulsion in childhood;Convulsions local;Convulsive threshold lowered;Coombs positive haemolytic anaemia;Coronary artery disease;Coronary artery embolism;Coronary artery thrombosis;Coronary bypass thrombosis;Coronavirus infection;Coronavirus test;Coronavirus test negative;Coronavirus test positive;Corpus callosotomy;Cough;Cough variant asthma;COVID-19;COVID-19 immunisation;COVID-19 pneumonia;COVID-19 prophylaxis;COVID-19 treatment;Cranial nerve disorder;Cranial nerve palsies multiple;Cranial nerve paralysis;CREST syndrome;Crohn's disease;Cryofibrinogenaemia;Cryoglobulinaemia;CSF oligoclonal band present;CSWS syndrome;Cutaneous amyloidosis;Cutaneous lupus erythematosus;Cutaneous sarcoidosis;Cutaneous vasculitis;Cyanosis;Cyclic neutropenia;Cystitis interstitial;Cytokine release syndrome;Cytokine storm;De novo purine synthesis inhibitors associated acute inflammatory syndrome;Death neonatal;Deep vein thrombosis;Deep vein thrombosis postoperative;Deficiency of bile secretion;Deja vu;Demyelinating polyneuropathy;Demyelination;Dermatitis;Dermatitis bullous;Dermatitis herpetiformis;Dermatomyositis;Device embolisation;Device related thrombosis;Diabetes mellitus;Diabetic ketoacidosis;Diabetic mastopathy;Dialysis amyloidosis;Dialysis membrane reaction;Diastolic hypotension;Diffuse vasculitis;Digital pitting scar;Disseminated intravascular coagulation;Disseminated intravascular coagulation in newborn;Disseminated neonatal herpes simplex;Disseminated varicella;Disseminated varicella zoster vaccine virus infection;Disseminated varicella zoster virus infection;DNA antibody positive;Double cortex syndrome;Double stranded DNA antibody positive;Dreamy state;Dressler's syndrome;Drop attacks;Drug withdrawal convulsions;Dyspnoea;Early infantile epileptic encephalopathy with burst-suppression;Eclampsia;Eczema herpeticum;Embolia cutis medicamentosa;Embolic cerebellar infarction;Embolic cerebral infarction;Embolic pneumonia;Embolic stroke;Embolism;Embolism arterial;Embolism venous;Encephalitis;Encephalitis allergic;Encephalitis autoimmune;Encephalitis brain stem;Encephalitis haemorrhagic;Encephalitis periaxialis diffusa;Encephalitis post immunisation;Encephalomyelitis;Encephalopathy;Endocrine disorder;Endocrine ophthalmopathy;Endotracheal intubation;Enteritis;Enteritis leukopenic;Enterobacter pneumonia;Enterocolitis;Enteropathic spondylitis;Eosinopenia;Eosinophilic

fasciitis;Eosinophilic granulomatosis with polyangiitis;Eosinophilic oesophagitis;Epidermolysis;Epilepsy;Epilepsy surgery;Epilepsy with myoclonic-atonic seizures;Epileptic aura;Epileptic psychosis;Erythema;Erythema induratum;Erythema multiforme;Erythema nodosum;Evans syndrome;Exanthema subitum;Expanded disability status scale score decreased;Expanded disability status scale score increased;Exposure to communicable disease;Exposure to SARS-CoV-2;Eye oedema;Eye pruritus;Eye swelling;Eyelid oedema;Face oedema;Facial paralysis;Facial paresis;Faciobrachial dystonic seizure;Fat embolism;Febrile convulsion;Febrile infection-related epilepsy syndrome;Febrile neutropenia;Felty's syndrome;Femoral artery embolism;Fibrillary glomerulonephritis;Fibromyalgia;Flushing;Foaming at mouth;Focal cortical resection;Focal dyscognitive seizures;Foetal distress syndrome;Foetal placental thrombosis;Foetor hepaticus;Foreign body embolism;Frontal lobe epilepsy;Fulminant type 1 diabetes mellitus;Galactose elimination capacity test abnormal;Galactose elimination capacity test decreased;Gamma-glutamyltransferase abnormal;Gamma-glutamyltransferase increased;Gastritis herpes;Gastrointestinal amyloidosis;Gelastic seizure;Generalised onset non-motor seizure;Generalised tonic-clonic seizure;Genital herpes;Genital herpes simplex;Genital herpes zoster;Giant cell arteritis;Glomerulonephritis;Glomerulonephritis membranoproliferative;Glomerulonephritis membranous;Glomerulonephritis rapidly progressive;Glossopharyngeal nerve paralysis;Glucose transporter type 1 deficiency syndrome;Glutamate dehydrogenase increased;Glycocholic acid increased;GM2 gangliosidosis;Goodpasture's syndrome;Graft thrombosis;Granulocytopenia;Granulocytopenia neonatal;Granulomatosis with polyangiitis;Granulomatous dermatitis;Grey matter heterotopia;Guanase increased;Guillain-Barre syndrome;Haemolytic anaemia;Haemophagocytic lymphohistiocytosis;Haemorrhage;Haemorrhagic ascites;Haemorrhagic disorder;Haemorrhagic pneumonia;Haemorrhagic varicella syndrome;Haemorrhagic vasculitis;Hantavirus pulmonary infection;Hashimoto's encephalopathy;Hashitoxicosis;Hemimegalencephaly;Henoch-Schonlein purpura;Henoch-Schonlein purpura nephritis;Hepaplastin abnormal;Hepaplastin decreased;Heparin-induced thrombocytopenia;Hepatic amyloidosis;Hepatic artery embolism;Hepatic artery flow decreased;Hepatic artery thrombosis;Hepatic enzyme abnormal;Hepatic enzyme decreased;Hepatic enzyme increased;Hepatic fibrosis marker abnormal;Hepatic fibrosis marker increased;Hepatic function abnormal;Hepatic hydrothorax;Hepatic hypertrophy;Hepatic hypoperfusion;Hepatic lymphocytic infiltration;Hepatic mass;Hepatic pain;Hepatic sequestration;Hepatic vascular resistance increased;Hepatic vascular thrombosis;Hepatic vein embolism;Hepatic vein thrombosis;Hepatic venous pressure gradient abnormal;Hepatic venous pressure gradient increased;Hepatitis;Hepatobiliary scan abnormal;Hepatomegaly;Hepatosplenomegaly;Hereditary angioedema with C1 esterase inhibitor deficiency;Herpes dermatitis;Herpes gestationis;Herpes oesophagitis;Herpes ophthalmic;Herpes pharyngitis;Herpes sepsis;Herpes simplex;Herpes simplex cervicitis;Herpes simplex colitis;Herpes simplex encephalitis;Herpes simplex gastritis;Herpes simplex hepatitis;Herpes simplex meningitis;Herpes simplex meningoencephalitis;Herpes simplex meningomyelitis;Herpes simplex necrotising retinopathy;Herpes simplex oesophagitis;Herpes simplex otitis externa;Herpes simplex pharyngitis;Herpes simplex pneumonia;Herpes simplex reactivation;Herpes simplex sepsis;Herpes simplex viraemia;Herpes simplex virus conjunctivitis neonatal;Herpes simplex visceral;Herpes virus

infection;Herpes zoster;Herpes zoster cutaneous disseminated;Herpes zoster infection neurological;Herpes zoster meningitis;Herpes zoster meningoencephalitis;Herpes zoster meningomyelitis;Herpes zoster meningoradiculitis;Herpes zoster necrotising retinopathy;Herpes zoster oticus;Herpes zoster pharyngitis;Herpes zoster reactivation;Herpetic radiculopathy;Histone antibody positive;Hoigne's syndrome;Human herpesvirus 6 encephalitis;Human herpesvirus 6 infection;Human herpesvirus 6 infection reactivation;Human herpesvirus 7 infection;Human herpesvirus 8 infection;Hyperammonaemia;Hyperbilirubinaemia;Hypercholia;Hypergammaglobulinaemia benign monoclonal;Hyperglycaemic seizure;Hypersensitivity;Hypersensitivity vasculitis;Hyperthyroidism;Hypertransaminasaemia;Hyperventilation;Hypoalbuminaemia;Hypocalcaemic seizure;Hypogammaglobulinaemia;Hypoglossal nerve paralysis;Hypoglossal nerve paresis;Hypoglycaemic seizure;Hyponatraemic seizure;Hypotension;Hypotensive crisis;Hypothenar hammer syndrome;Hypothyroidism;Hypoxia;Idiopathic CD4 lymphocytopenia;Idiopathic generalised epilepsy;Idiopathic interstitial pneumonia;Idiopathic neutropenia;Idiopathic pulmonary fibrosis;IgA nephropathy;IgM nephropathy;IIIrd nerve paralysis;IIIrd nerve paresis;Iliac artery embolism;Immune thrombocytopenia;Immune-mediated adverse reaction;Immune-mediated cholangitis;Immune-mediated cholestasis;Immune-mediated cytopenia;Immune-mediated encephalitis;Immune-mediated encephalopathy;Immune-mediated endocrinopathy;Immune-mediated enterocolitis;Immune-mediated gastritis;Immune-mediated hepatic disorder;Immune-mediated hepatitis;Immune-mediated hyperthyroidism;Immune-mediated hypothyroidism;Immune-mediated myocarditis;Immune-mediated myositis;Immune-mediated nephritis;Immune-mediated neuropathy;Immune-mediated pancreatitis;Immune-mediated pneumonitis;Immune-mediated renal disorder;Immune-mediated thyroiditis;Immune-mediated uveitis;Immunoglobulin G4 related disease;Immunoglobulins abnormal;Implant site thrombosis;Inclusion body myositis;Infantile genetic agranulocytosis;Infantile spasms;Infected vasculitis;Infective thrombosis;Inflammation;Inflammatory bowel disease;Infusion site thrombosis;Infusion site vasculitis;Injection site thrombosis;Injection site urticaria;Injection site vasculitis;Instillation site thrombosis;Insulin autoimmune syndrome;Interstitial granulomatous dermatitis;Interstitial lung disease;Intracardiac mass;Intracardiac thrombus;Intracranial pressure increased;Intrapericardial thrombosis;Intrinsic factor antibody abnormal;Intrinsic factor antibody positive;IPEX syndrome;Irregular breathing;IRVAN syndrome;IVth nerve paralysis;IVth nerve paresis;JC polyomavirus test positive;JC virus CSF test positive;Jeavons syndrome;Jugular vein embolism;Jugular vein thrombosis;Juvenile idiopathic arthritis;Juvenile myoclonic epilepsy;Juvenile polymyositis;Juvenile psoriatic arthritis;Juvenile spondyloarthritis;Kaposi sarcoma inflammatory cytokine syndrome;Kawasaki's disease;Kayser-Fleischer ring;Keratoderma blenorrhagica;Ketosis-prone diabetes mellitus;Kounis syndrome;Lafora's myoclonic epilepsy;Lamb's excrescences;Laryngeal dyspnoea;Laryngeal oedema;Laryngeal rheumatoid arthritis;Laryngospasm;Laryngotracheal oedema;Latent autoimmune diabetes in adults;LE cells present;Lemierre syndrome;Lennox-Gastaut syndrome;Leucine aminopeptidase increased;Leukoencephalomyelitis;Leukoencephalopathy;Leukopenia;Leukopenia neonatal;Lewis-Sumner syndrome;Lhermitte's sign;Lichen planopilaris;Lichen planus;Lichen sclerosus;Limbic encephalitis;Linear IgA disease;Lip oedema;Lip swelling;Liver function test abnormal;Liver function test decreased;Liver function test increased;Liver induration;Liver injury;Liver iron concentration abnormal;Liver iron concentration

increased;Liver opacity;Liver palpable;Liver sarcoidosis;Liver scan abnormal;Liver tenderness;Low birth weight baby;Lower respiratory tract herpes infection;Lower respiratory tract infection;Lower respiratory tract infection viral;Lung abscess;Lupoid hepatic cirrhosis;Lupus cystitis;Lupus encephalitis;Lupus endocarditis;Lupus enteritis;Lupus hepatitis;Lupus myocarditis;Lupus myositis;Lupus nephritis;Lupus pancreatitis;Lupus pleurisy;Lupus pneumonitis;Lupus vasculitis;Lupus-like syndrome;Lymphocytic hypophysitis;Lymphocytopenia neonatal;Lymphopenia;MAGIC syndrome;Magnetic resonance imaging liver abnormal;Magnetic resonance proton density fat fraction measurement;Mahler sign;Manufacturing laboratory analytical testing issue;Manufacturing materials issue;Manufacturing production issue;Marburg's variant multiple sclerosis;Marchiafava-Bignami disease;Marine Lenhart syndrome;Mastocytic enterocolitis;Maternal exposure during pregnancy;Medical device site thrombosis;Medical device site vasculitis;MELAS syndrome;Meningitis;Meningitis aseptic;Meningitis herpes;Meningoencephalitis herpes simplex neonatal;Meningoencephalitis herpetic;Meningomyelitis herpes;MERS-CoV test;MERS-CoV test negative;MERS-CoV test positive;Mesangioproliferative glomerulonephritis;Mesenteric artery embolism;Mesenteric artery thrombosis;Mesenteric vein thrombosis;Metapneumovirus infection;Metastatic cutaneous Crohn's disease;Metastatic pulmonary embolism;Microangiopathy;Microembolism;Microscopic polyangiitis;Middle East respiratory syndrome;Migraine-triggered seizure;Miliary pneumonia;Miller Fisher syndrome;Mitochondrial aspartate aminotransferase increased;Mixed connective tissue disease;Model for end stage liver disease score abnormal;Model for end stage liver disease score increased;Molar ratio of total branched-chain amino acid to tyrosine;Molybdenum cofactor deficiency;Monocytopenia;Mononeuritis;Mononeuropathy multiplex;Morphoea;Morvan syndrome;Mouth swelling;Moyamoya disease;Multifocal motor neuropathy;Multiple organ dysfunction syndrome;Multiple sclerosis;Multiple sclerosis relapse;Multiple sclerosis relapse prophylaxis;Multiple subpial transection;Multisystem inflammatory syndrome in children;Muscular sarcoidosis;Myasthenia gravis;Myasthenia gravis crisis;Myasthenia gravis neonatal;Myasthenic syndrome;Myelitis;Myelitis transverse;Myocardial infarction;Myocarditis;Myocarditis post infection;Myoclonic epilepsy;Myoclonic epilepsy and ragged-red fibres;Myokymia;Myositis;Narcolepsy;Nasal herpes;Nasal obstruction;Necrotising herpetic retinopathy;Neonatal Crohn's disease;Neonatal epileptic seizure;Neonatal lupus erythematosus;Neonatal mucocutaneous herpes simplex;Neonatal pneumonia;Neonatal seizure;Nephritis;Nephrogenic systemic fibrosis;Neuralgic amyotrophy;Neuritis;Neuritis cranial;Neuromyelitis optica pseudo relapse;Neuromyelitis optica spectrum disorder;Neuromyotonia;Neuronal neuropathy;Neuropathy peripheral;Neuropathy, ataxia, retinitis pigmentosa syndrome;Neuropsychiatric lupus;Neurosarcoidosis;Neutropenia;Neutropenia neonatal;Neutropenic colitis;Neutropenic infection;Neutropenic sepsis;Nodular rash;Nodular vasculitis;Noninfectious myelitis;Noninfective encephalitis;Noninfective encephalomyelitis;Noninfective oophoritis;Obstetrical pulmonary embolism;Occupational exposure to communicable disease;Occupational exposure to SARS-CoV-2;Ocular hyperaemia;Ocular myasthenia;Ocular pemphigoid;Ocular sarcoidosis;Ocular vasculitis;Oculofacial paralysis;Oedema;Oedema blister;Oedema due to hepatic disease;Oedema mouth;Oesophageal achalasia;Ophthalmic artery thrombosis;Ophthalmic herpes simplex;Ophthalmic herpes zoster;Ophthalmic vein thrombosis;Optic neuritis;Optic

neuropathy; Optic perineuritis; Oral herpes; Oral lichen planus; Oropharyngeal oedema; Oropharyngeal spasm; Oropharyngeal swelling; Osmotic demyelination syndrome; Ovarian vein thrombosis; Overlap syndrome; Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection; Paget-Schroetter syndrome; Palindromic rheumatism; Palisaded neutrophilic granulomatous dermatitis; Palmoplantar keratoderma; Palpable purpura; Pancreatitis; Panencephalitis; Papillophlebitis; Paracancerous pneumonia; Paradoxical embolism; Parainfluenzae viral laryngotracheobronchitis; Paraneoplastic dermatomyositis; Paraneoplastic pemphigus; Paraneoplastic thrombosis; Paresis cranial nerve; Parietal cell antibody positive; Paroxysmal nocturnal haemoglobinuria; Partial seizures; Partial seizures with secondary generalisation; Patient isolation; Pelvic venous thrombosis; Pemphigoid; Pemphigus; Penile vein thrombosis; Pericarditis; Pericarditis lupus; Perihepatic discomfort; Periorbital oedema; Periorbital swelling; Peripheral artery thrombosis; Peripheral embolism; Peripheral ischaemia; Peripheral vein thrombus extension; Periportal oedema; Peritoneal fluid protein abnormal; Peritoneal fluid protein decreased; Peritoneal fluid protein increased; Peritonitis lupus; Pernicious anaemia; Petit mal epilepsy; Pharyngeal oedema; Pharyngeal swelling; Pityriasis lichenoides et varioliformis acuta; Placenta praevia; Pleuroparenchymal fibroelastosis; Pneumobilia; Pneumonia; Pneumonia adenoviral; Pneumonia cytomegaloviral; Pneumonia herpes viral; Pneumonia influenzal; Pneumonia measles; Pneumonia mycoplasmal; Pneumonia necrotising; Pneumonia parainfluenzae viral; Pneumonia respiratory syncytial viral; Pneumonia viral; POEMS syndrome; Polyarteritis nodosa; Polyarthritides; Polychondritis; Polyglandular autoimmune syndrome type I; Polyglandular autoimmune syndrome type II; Polyglandular autoimmune syndrome type III; Polyglandular disorder; Polymicrogyria; Polymyalgia rheumatica; Polymyositis; Polyneuropathy; Polyneuropathy idiopathic progressive; Portal pyaemia; Portal vein embolism; Portal vein flow decreased; Portal vein pressure increased; Portal vein thrombosis; Portosplenomesenteric venous thrombosis; Post procedural hypotension; Post procedural pneumonia; Post procedural pulmonary embolism; Post stroke epilepsy; Post stroke seizure; Post thrombotic retinopathy; Post thrombotic syndrome; Post viral fatigue syndrome; Postictal headache; Postictal paralysis; Postictal psychosis; Postictal state; Postoperative respiratory distress; Postoperative respiratory failure; Postoperative thrombosis; Postpartum thrombosis; Postpartum venous thrombosis; Postpericardiotomy syndrome; Post-traumatic epilepsy; Postural orthostatic tachycardia syndrome; Precerebral artery thrombosis; Pre-eclampsia; Preictal state; Premature labour; Premature menopause; Primary amyloidosis; Primary biliary cholangitis; Primary progressive multiple sclerosis; Procedural shock; Proctitis herpes; Proctitis ulcerative; Product availability issue; Product distribution issue; Product supply issue; Progressive facial hemiatrophy; Progressive multifocal leukoencephalopathy; Progressive multiple sclerosis; Progressive relapsing multiple sclerosis; Prosthetic cardiac valve thrombosis; Pruritus; Pruritus allergic; Pseudovasculitis; Psoriasis; Psoriatic arthropathy; Pulmonary amyloidosis; Pulmonary artery thrombosis; Pulmonary embolism; Pulmonary fibrosis; Pulmonary haemorrhage; Pulmonary microemboli; Pulmonary oil microembolism; Pulmonary renal syndrome; Pulmonary sarcoidosis; Pulmonary sepsis; Pulmonary thrombosis; Pulmonary tumour thrombotic microangiopathy; Pulmonary vasculitis; Pulmonary veno-occlusive disease; Pulmonary venous thrombosis; Pyoderma gangrenosum; Pyostomatitis vegetans; Pyrexia; Quarantine; Radiation leukopenia; Radiculitis

brachial;Radiologically isolated syndrome;Rash;Rash erythematous;Rash pruritic;Rasmussen encephalitis;Raynaud's phenomenon;Reactive capillary endothelial proliferation;Relapsing multiple sclerosis;Relapsing-remitting multiple sclerosis;Renal amyloidosis;Renal arteritis;Renal artery thrombosis;Renal embolism;Renal failure;Renal vascular thrombosis;Renal vasculitis;Renal vein embolism;Renal vein thrombosis;Respiratory arrest;Respiratory disorder;Respiratory distress;Respiratory failure;Respiratory paralysis;Respiratory syncytial virus bronchiolitis;Respiratory syncytial virus bronchitis;Retinal artery embolism;Retinal artery occlusion;Retinal artery thrombosis;Retinal vascular thrombosis;Retinal vasculitis;Retinal vein occlusion;Retinal vein thrombosis;Retinol binding protein decreased;Retinopathy;Retrograde portal vein flow;Retroperitoneal fibrosis;Reversible airways obstruction;Reynold's syndrome;Rheumatic brain disease;Rheumatic disorder;Rheumatoid arthritis;Rheumatoid factor increased;Rheumatoid factor positive;Rheumatoid factor quantitative increased;Rheumatoid lung;Rheumatoid neutrophilic dermatosis;Rheumatoid nodule;Rheumatoid nodule removal;Rheumatoid scleritis;Rheumatoid vasculitis;Saccadic eye movement;SAPHO syndrome;Sarcoidosis;SARS-CoV-1 test;SARS-CoV-1 test negative;SARS-CoV-1 test positive;SARS-CoV-2 antibody test;SARS-CoV-2 antibody test negative;SARS-CoV-2 antibody test positive;SARS-CoV-2 carrier;SARS-CoV-2 sepsis;SARS-CoV-2 test;SARS-CoV-2 test false negative;SARS-CoV-2 test false positive;SARS-CoV-2 test negative;SARS-CoV-2 test positive;SARS-CoV-2 viraemia;Satoyoshi syndrome;Schizencephaly;Scleritis;Sclerodactylia;Scleroderma;Scleroderma associated digital ulcer;Scleroderma renal crisis;Scleroderma-like reaction;Secondary amyloidosis;Secondary cerebellar degeneration;Secondary progressive multiple sclerosis;Segmented hyalinising vasculitis;Seizure;Seizure anoxic;Seizure cluster;Seizure like phenomena;Seizure prophylaxis;Sensation of foreign body;Septic embolus;Septic pulmonary embolism;Severe acute respiratory syndrome;Severe myoclonic epilepsy of infancy;Shock;Shock symptom;Shrinking lung syndrome;Shunt thrombosis;Silent thyroiditis;Simple partial seizures;Sjogren's syndrome;Skin swelling;SLE arthritis;Smooth muscle antibody positive;Sneezing;Spinal artery embolism;Spinal artery thrombosis;Splenic artery thrombosis;Splenic embolism;Splenic thrombosis;Splenic vein thrombosis;Spondylitis;Spondyloarthropathy;Spontaneous heparin-induced thrombocytopenia syndrome;Status epilepticus;Stevens-Johnson syndrome;Stiff leg syndrome;Stiff person syndrome;Stillbirth;Still's disease;Stoma site thrombosis;Stoma site vasculitis;Stress cardiomyopathy;Stridor;Subacute cutaneous lupus erythematosus;Subacute endocarditis;Subacute inflammatory demyelinating polyneuropathy;Subclavian artery embolism;Subclavian artery thrombosis;Subclavian vein thrombosis;Sudden unexplained death in epilepsy;Superior sagittal sinus thrombosis;Susac's syndrome;Suspected COVID-19;Swelling;Swelling face;Swelling of eyelid;Swollen tongue;Sympathetic ophthalmia;Systemic lupus erythematosus;Systemic lupus erythematosus disease activity index abnormal;Systemic lupus erythematosus disease activity index decreased;Systemic lupus erythematosus disease activity index increased;Systemic lupus erythematosus rash;Systemic scleroderma;Systemic sclerosis pulmonary;Tachycardia;Tachypnoea;Takayasu's arteritis;Temporal lobe epilepsy;Terminal ileitis;Testicular autoimmunity;Throat tightness;Thromboangiitis obliterans;Thrombocytopenia;Thrombocytopenic purpura;Thrombophlebitis;Thrombophlebitis migrans;Thrombophlebitis

neonatal;Thrombophlebitis septic;Thrombophlebitis superficial;Thromboplastin antibody positive;Thrombosis;Thrombosis corpora cavernosa;Thrombosis in device;Thrombosis mesenteric vessel;Thrombotic cerebral infarction;Thrombotic microangiopathy;Thrombotic stroke;Thrombotic thrombocytopenic purpura;Thyroid disorder;Thyroid stimulating immunoglobulin increased;Thyroiditis;Tongue amyloidosis;Tongue biting;Tongue oedema;Tonic clonic movements;Tonic convulsion;Tonic posturing;Topectomy;Total bile acids increased;Toxic epidermal necrolysis;Toxic leukoencephalopathy;Toxic oil syndrome;Tracheal obstruction;Tracheal oedema;Tracheobronchitis;Tracheobronchitis mycoplasmal;Tracheobronchitis viral;Transaminases abnormal;Transaminases increased;Transfusion-related alloimmune neutropenia;Transient epileptic amnesia;Transverse sinus thrombosis;Trigeminal nerve paresis;Trigeminal neuralgia;Trigeminal palsy;Truncus coeliacus thrombosis;Tuberous sclerosis complex;Tubulointerstitial nephritis and uveitis syndrome;Tumefactive multiple sclerosis;Tumour embolism;Tumour thrombosis;Type 1 diabetes mellitus;Type I hypersensitivity;Type III immune complex mediated reaction;Uhthoff's phenomenon;Ulcerative keratitis;Ultrasound liver abnormal;Umbilical cord thrombosis;Uncinate fits;Undifferentiated connective tissue disease;Upper airway obstruction;Urine bilirubin increased;Urobilinogen urine decreased;Urobilinogen urine increased;Urticaria;Urticaria papular;Urticarial vasculitis;Uterine rupture;Uveitis;Vaccination site thrombosis;Vaccination site vasculitis;Vagus nerve paralysis;Varicella;Varicella keratitis;Varicella post vaccine;Varicella zoster gastritis;Varicella zoster oesophagitis;Varicella zoster pneumonia;Varicella zoster sepsis;Varicella zoster virus infection;Vasa praevia;Vascular graft thrombosis;Vascular pseudoaneurysm thrombosis;Vascular purpura;Vascular stent thrombosis;Vasculitic rash;Vasculitic ulcer;Vasculitis;Vasculitis gastrointestinal;Vasculitis necrotising;Vena cava embolism;Vena cava thrombosis;Venous intravasation;Venous recanalisation;Venous thrombosis;Venous thrombosis in pregnancy;Venous thrombosis limb;Venous thrombosis neonatal;Vertebral artery thrombosis;Vessel puncture site thrombosis;Visceral venous thrombosis;VIth nerve paralysis;VIth nerve paresis;Vitiligo;Vocal cord paralysis;Vocal cord paresis;Vogt-Koyanagi-Harada disease;Warm type haemolytic anaemia;Wheezing;White nipple sign;XIth nerve paralysis;X-ray hepatobiliary abnormal;Young's syndrome;Zika virus associated Guillain Barre syndrome.

ANNEX

**List of \$350 Million in Secret Payments to Fauci,
Collins, Others at NIH**

NIH Royalty Disclosures FY2010-FY2014



Top line numbers:

Time period: **FY2010 to FY 2014**

Number of scientists named: **1,675**

Number of payments made: **22,064**

The top five scientists by number of payments and agency affiliation. Only Ira Pastan is still employed with NIH:

1 Robert Gallo, National Cancer Institute, 271 payments

2 Ira Pastan, National Cancer Institute, 250 payments

3 Mikulas Popovic, National Cancer Institute, 191 payments

4 Flossie Wong-Staal, National Cancer Institute, 190 payments

5 Mangalasseril Sarngadharan, National Cancer Institute, 188 payments

Anthony Fauci: 23 payments

Clifford Lane, NIAID Deputy Director for Clinical Research and Special Projects: 8 payments

Francis Collins, NIH director from 2009-2021: 14 payments

Top Agency Payments:

Agency Names	payments
NCI	112,976,379.84
NIAID	9,311,705.53
NEI	2,183,063.20
NHLBI	1,741,074.55
NICHHD	1,295,775.14
	Total: \$127,507,998.26

NCI: National Cancer Institute

NIAID: National Institute of Allergy and Infectious Diseases

NEI: National Eye Institute

NHLBI: National Heart, Lung, and Blood Institute

NICHHD: National Institute of Child Health and Human Development

Total amount paid: **\$134,027,668.6** (note some agencies have redacted totals so this is less than true total)

Payments by agency by year (note some agencies have redacted totals so this is less than true total)

FY2010: \$18,791,296.99

FY2011: \$22,444,175.55

FY2012: \$26,879,545.30

FY2013: \$30,462,168.86

FY2014: \$35,450,481.94

The four NIH agencies included but with redacted totals:

NCATS National Center for Advancing Translational Sciences

NIAAA National Institute on Alcohol Abuse and Alcoholism

FIC Fogarty International Center

NCCAM National Center for Complementary and Alternative Medicine

- NCCAM is now called NCCIH, National Center for Complementary and Integrative Health

The National Institute of Health is resisting every effort to bring transparency to millions of dollars in royalty payments its research scientists receive every year in addition to their salaries. The U.S. Department of Health and Human Services began developing guidance for collecting and publishing royalty data from NIH researchers over twenty years ago. This data, however, is not publicly available.

NIH is still not disclosing information about what companies are using patents developed at the NIH, and which researchers are getting paid for them. OpenTheBooks.com sued the agency to release these documents under a Freedom of Information Act request, but documents received so far are highly redacted and over a decade old.

Patent Payouts

The National Institute of Health, part of the U.S. Department of Health and Human Services, is the [largest](#) biomedical research agency in the world. NIH grants over [\\$32 billion](#) in funding to research institutions around the world, and employs [thousands](#) of scientists to conduct research in-house.

When an NIH employee makes a discovery in their official capacity, the NIH [owns](#) the rights to any resulting patent. These patents are then licensed for commercial use to companies that could use them to bring products to market. Employees are listed as inventors on the patents and receive a share of the royalties obtained through any licensing, or “technology transfer,” of their inventions.

Essentially, taxpayer money funding NIH research benefits researchers employed by NIH because they are listed as patent inventors and therefore receive royalty payments from licensees.

Researchers could be involved in experiments using technology they invented, furthering the application and commercial viability of that technology, which may or may not be in the public's best interest.

Inventors receive the first \$2,000 collected from a licensee. Next, they receive 15 percent of royalties above \$2,000 and up to \$50,000. Finally, they receive 25 percent of royalties in excess of the first \$50,000 collected each year. Each inventor cannot receive more than \$150,000 in royalty payments for a calendar year.

Understanding Conflict of Interests: Patients

The HHS came under fire in 1999 when a young man died while undergoing experimental gene therapy treatment at the University of Pennsylvania for an NIH Office of Biotechnology Activities clinical trial.

An investigation showed [many](#) administrative failures and irregularities leading up to his death, including a financial conflict of interest; a principal investigator owned shares in a company that would benefit from the experimental technology.

In response to the tragedy and broader concerns with ethics in clinical trials at the agency, in 2000 then-HHS Secretary Donna Shalala [pledged](#) reforms to better protect patients involved in research experiments.

HHS guidance released in 2001 [outlined](#) steps that had to be taken by the agency to achieve these goals.

One reform enhanced transparency in researchers' financial conflicts of interest—if a researcher stood to financially gain from experiments involving humans, their patients had to know.

In 2005 an explosive investigation by the Associated Press [found](#) the NIH had not yet provided these financial disclosures to patients. Through Freedom of Information Act requests, AP found over 900 NIH researchers collected \$8.9 million in 2004.

AP also discovered that 51 NIH royalty recipients were then working on experiments involving inventions for which they were being paid.

[Among](#) those 51 was Anthony Fauci, then- and current director of the National Institute of Allergy and Infectious Diseases, who had received \$45,072.82 between 1997 and 2004 for a patent license on an experimental AIDS treatment.

At the time, Fauci expressed confusion and frustration regarding conflict of interest disclosure at NIH, noting he donated all proceeds from the royalties to charity.

Shortly after AP filed the FOIA request in 2004 for the royalty payments NIH scientists receive from patents, NIH released new [guidelines](#) on such financial disclosures.

Understanding Conflict of Interests: The Public

Patients involved in clinical trials can now benefit from information regarding a researcher's potential conflict of interests.

But the public that funds this research, and the lawmakers that provide oversight to these agencies, are in many ways still in the dark.

The U.S. Government Accountability Office released a [report](#) in 2020 titled “NIH Should Publicly Report More Information about the Licensing of Its Intellectual Property.”

The report identified 4,446 U.S. patents owned by HHS, but focused only on patents that contributed to the development of drugs approved by the FDA.

In total, 93 NIH patents contributed to 34 FDA-approved drugs. The NIH granted 32 licenses to pharmaceutical companies based on these patents, which generated about \$2 billion in royalty payments to the agency between 1991-2019.

GAO highlighted the importance of transparency in maintaining trust and improving understanding of the research process.

Because the HHS funds billions of dollars in research a year, primarily through NIH, there are concerns regarding how private companies benefit from this research, particularly regarding how much they charge for therapies created using taxpayer funds. There are also concerns related to how the FDA, another HHS agency, approves treatments that NIH scientists contribute to.

Licensing and royalty transparency could help policymakers and the public understand the complicated nexus between federal research and regulatory agencies and the private sector.

GAO made several recommendations to improve transparency, [including](#) to “publicly report information [regarding licensing outcomes and impacts] in an accessible and searchable format to the maximum extent possible.”

The NIH responded by listing all of its “active U.S. patents” on a webpage. [Thousands](#) of patents are listed, broken out by institute, but licensee, inventor, and royalty information are not included.

Agency officials also told GAO they “are working to deploy a new enterprise technology transfer system that will allow them to publish additional information on active commercial licenses,” but have not yet.

Opening the Books on NIH Royalty Payments

Over the past 20 years the HHS has proven it is in no rush to make financial disclosures at the agency more transparent.

In September 2021 OpenTheBooks.com filed FOIA requests with NIH [asking](#) for a complete list/database of all personal royalties paid to current and former National Institutes of Health employees for work done while they were federally employed.

We specified that the list/database should include the royalty recipient's name, the amount of the royalty, the reason for the royalty, the date the royalty was paid, and the name of the entity paying the royalty.

NIH failed to comply with this request, so we partnered with Judicial Watch to sue for these documents in October 2021.

In response to the lawsuit, NIH began producing approximately 300 pages in royalty payments a month, starting in February 2022.

The documents we have received so far have been heavily redacted, only revealing most (but not all) of the names of the researchers receiving payments, how many payments they received, and how much money each NIH institute has collected in royalties.

According to NIH Freedom of Information Officer Karen E. Lampe-S, redactions were made under three exemptions:

- The Federal Transfer and Technology Act, 15 USC 3710a(c)(7)(A), prohibits federal agencies from disclosing commercial or financial information, including royalty information, obtained from parties participating in technology transfer with Federal Agencies.
- Protecting disclosure trade secrets and commercial or financial information that is privileged and confidential.
- Permitting the withholding of privacy information, the release of which would constitute a clearly unwarranted invasion of personal privacy.

The NIH redacted all information regarding how much researchers are being paid and what licensees are paying these royalties. We asked for all documentation up to 2020 or later, but the first documents we received so far, about 1,200 pages, are from October 2009 to September 2014.

While most pages were machine-readable, several pages documenting the frequency of payments were not, and so could not be included in our analysis.

Still, we can make some interesting observations based on the data we do have.

During the time period covered in these documents, **October 2009 to September 2014**, NIH inventors received over \$134 million in royalty payments. Over **1,600** different scientists were named as personally receiving royalty payments during this time. More names and payment amounts were redacted, however, and could not be included in these counts.

The top five scientists receiving royalty payments and the institutes they were affiliated with are as follows. Only Ira Pastan is still employed with NIH:

- 1 Robert Charles Gallo, National Cancer Institute, 271 payments
- 2 Ira Pastan, National Cancer Institute, 250 payments
- 3 Mikulas Popovic, National Cancer Institute, 191 payments
- 4 Flossie Wong-Staal, National Cancer Institute, 190 payments
- 5 Mangalasseril Sarngadharan, National Cancer Institute, 188 payments

*Note these only indicate frequency of payments. There is no way to know the payment amount because of how these documents are redacted. Frequency numbers may also be under-counted due to irregularities in machine-readability of documents.

Anthony Fauci, perhaps the most famous NIH employee and the highest-salaried person in the federal government, received 23 payments. Francis Collins, NIH director from 2009-2021, received 14.

21 of NIH's 27 institutes and centers reported royalty income, along with the FDA. The FDA is not an NIH agency but formed a joint council with the NIH in [2010](#) to strengthen collaboration. The institute reporting the most income from royalty payments during this time is the National Cancer Institute, with \$112,976,379. Four institutes reported income that was redacted.

While the documents we have received so far are illuminating, we need more information to understand the full ecosystem of royalty payments and federally-funded scientific research. We will be regularly updating our readers with new findings as we collect more documents.

Vaccine Excipient & Media Summary

Vaccine Excipient & Media Summary, Part 2

Excipients Included in U.S. Vaccines, by Vaccine

Vaccine	Contains
Anthrax (BioThrax)	Aluminum Hydroxide, Amino Acids, Benzethonium Chloride, Formaldehyde or Formalin, Sodium Chloride, Vitamins (unspecified)
BCG (Tice)	Lactose, Sodium Chloride
DTaP (DAPTACEL)	Aluminum Phosphate, Aluminum Potassium Sulfate, Formaldehyde or Formalin, 2-Phenoxyethanol
DTaP (Infanrix)	Aluminum Hydroxide, Formaldehyde or Formalin, Glutaraldehyde, 2-Phenoxyethanol, Polysorbate 80
DTaP (Tripedia)	Aluminum Potassium Sulfate, Formaldehyde or Formalin, Gelatin, Polysorbate 80, Thimerosal*
DTaP (Most brands)	Hydrochloric Acid, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate)
DTaP/Hib (TriHIBit)	Aluminum Potassium Sulfate, Ammonium Sulfate, Formaldehyde or Formalin, Gelatin, Polysorbate 80, Sucrose, Thimerosal*
DTaP/HepB/IPV (Pediarix)	Aluminum Hydroxide, Formaldehyde or Formalin, Glutaraldehyde, Neomycin, 2-Phenoxyethanol, Polymyxin B, Polysorbate 80, Thimerosal*, Yeast Protein
DT (Aventis)	Aluminum Potassium Sulfate, Formaldehyde or Formalin
DT (Massachusetts)	Aluminum Hydroxide, Formaldehyde or Formalin
DT (Some brands)	Glycine, Hydrochloric Acid, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Sodium Acetate, Sodium Hydroxide, Thimerosal (some multidose containers)
Hib (ACTHib)	Ammonium Sulfate, Formaldehyde or Formalin, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Sucrose
Hib (PedvaxHib)	Aluminum Hydroxyphosphate Sulfate, Sodium Chloride
Hib (HibTITER)	Yeast Protein
Hib (Some packages)	Lactose
Hib/Hep B (Comvax)	Formaldehyde or Formalin, Sodium Borate, Yeast Protein
Hep A (Havrix)	Bovine Albumin or Serum, Aluminum Hydroxide, Amino Acids, Formaldehyde or Formalin, MRC-5 Cellular Protein, 2-Phenoxyethanol, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Polysorbate 20
Hep A (Vaqta)	Bovine Albumin or Serum, DNA, Formaldehyde or Formalin, MRC-5 Cellular Protein, Sodium Borate
Hep B (Engerix-B)	Aluminum Hydroxide, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Thimerosal*, Yeast Protein

Vaccine	Contains
Hep B (Recombivax)	Yeast Protein
HepA/HepB (Twinrix)	Aluminum Hydroxide, Aluminum Phosphate, Amino Acids, Formaldehyde or Formalin, MRC-5 Cellular Protein, Neomycin, 2-Phenoxyethanol, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Polysorbate 20, Thimerosal*, Yeast Protein
Influenza (Fluarix)	Egg Albumin (Ovalbumin), Egg Protein, Formaldehyde or Formalin, Gentamicin, Hydrocortisone, Octoxynol-10, α -Tocopheryl Hydrogen Succinate, Polysorbate 80, Sodium Deoxycholate, Thimerosal*
Influenza (Fluvirin)	Beta-Propiolactone, Egg Protein, Neomycin, Polymyxin B, Polyoxyethylene 9-10 Nonyl Phenol (Triton N-101, Octoxynol 9), Thimerosal (multidose containers)
Influenza (Fluzone)	Egg Protein, Formaldehyde or Formalin, Gelatin, Polyethylene glycol p-isooctylphenyl ether (Triton X-100), Thimerosal (multidose containers)
Influenza (FluMist)	Egg Protein, Gentamicin, Monosodium Glutamate, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Sucrose
Influenza (varies seasonally)	Bactopeptone
IPV (Ipol)	Formaldehyde or Formalin, Neomycin, 2-Phenoxyethanol, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Polymyxin B, Sodium Chloride, Streptomycin
Japanese Encephalitis (JE-Vax)	Formaldehyde or Formalin, Gelatin, Mouse Serum Protein, Thimerosal
Measles (Attenuvax)	Human Serum Albumin, Bovine Albumin or Serum, Gelatin, Neomycin, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Sodium Chloride, Sorbitol, Sucrose
Meningococcal (Menactra)	Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Sodium Chloride
Meningococcal (Menomune)	Lactose, Thimerosal (10-dose vials only)
Mumps (Mumpsvax)	Human Serum Albumin, Bovine Albumin or Serum, Gelatin, Neomycin, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Sodium Chloride, Sorbitol, Sucrose
MMR (MMR-II)	Human Serum Albumin, Bovine Albumin or Serum, Gelatin, Neomycin, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Sodium Chloride, Sorbitol, Sucrose
MMRV (ProQuad)	Sucrose, Gelatin, Sodium Chloride, Sorbitol, Monosodium L-glutamate, Human Serum Albumin, MRC-5 Cellular Protein, Neomycin, Bovine Albumin or Serum, Sodium Phosphate Dibasic, Sodium Bicarbonate, Potassium Phosphate Monobasic, Potassium Chloride, Potassium Phosphate Dibasic
Pneumococcal (Pneumovax)	Phenol, Sodium Chloride
Pneumococcal (Prevnar)	Aluminum Phosphate, Sodium Chloride

Vaccine	Contains
Rabies (Biorab)	Aluminum Phosphate, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Sodium Chloride, Thimerosal
Rabies (Imovax)	Human Serum Albumin, Bovine Albumin or Serum, Beta-Propiolactone, MRC-5 Cellular Protein, Neomycin, Phenol Red (Phenolsulfonphthalein), Sodium Chloride, Vitamins (unspecified)
Rabies (RabAvert)	Egg Albumin (Ovalbumin), Bovine Albumin or Serum, Amphotericin B, Beta-Propiolactone, Chlortetracycline, Ethylenediamine-Tetraacetic Acid Sodium (EDTA), Gelatin, Neomycin, Potassium Glutamate, Sodium Chloride
Rubella (Meruvax II)	Human Serum Albumin, Bovine Albumin or Serum, Gelatin, Neomycin, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Sodium Chloride, Sorbitol
Td (Decavac)	Aluminum Phosphate, Amino Acids, Formaldehyde or Formalin, 2-Phenoxyethanol, Thimerosal (some multidose containers), Vitamins (unspecified)
Td (Massachusetts)	Aluminum Hydroxide, Aluminum Phosphate, Formaldehyde or Formalin, Thimerosal (some multidose containers)
Td (Some Brands)	Glycine, Sodium Acetate, Sodium Hydroxide
Tdap (Adacel)	Aluminum Phosphate, Formaldehyde or Formalin, Glutaraldehyde, 2-Phenoxyethanol, Sodium Chloride
Tdap (Boostrix)	Aluminum Hydroxide, Formaldehyde or Formalin, Glutaraldehyde, Polysorbate 80
Typhoid (inactivated – Typhim Vi)	Phenol, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Polydimethylsiloxane, Sodium Chloride
Typhoid (oral – TY21a)	Amino Acids, Ascorbic Acid, Gelatin, Lactose, Magnesium Stearate, Sucrose
Vaccinia (DryVax)	Bovine Albumin or Serum, Brilliant Green (historic), Chlortetracycline, Glycerin, Neomycin, Phenol, Polymyxin B, Streptomycin, Urea (refrigerator-stable formulation only)
Varicella (Varivax)	Bovine Albumin or Serum, Ethylenediamine-Tetraacetic Acid Sodium (EDTA), Gelatin, Monosodium Glutamate, MRC-5 Cellular Protein, Neomycin, Phosphate Buffers (e.g., disodium, monosodium, potassium, sodium dihydrogen phosphate), Sodium Chloride, Sucrose
Yellow Fever (YF-Vax)	Egg Protein, Gelatin, Sodium Chloride, Sorbitol

Where “thimerosal” is marked with an asterisk () it indicates that the product should be considered equivalent to thimerosal-free products. This vaccine may contain trace amounts (<3 mcg) of mercury left after post-production thimerosal removal, but these amounts have no biological effect.

JAMA 1999;282(18) and *JAMA* 2000;283(16)

Adapted from Grabenstein JD. *ImmunoFacts: Vaccines & Immunologic Drugs*. St. Louis, MO: Wolters Kluwer Health Inc.; 2006 with additional content from individual products’ package inserts.



An international treaty on pandemic prevention and preparedness

Latest news

When a pandemic strikes, everyone is vulnerable.

Council gives green light to start negotiations on international pandemic treaty

On 3 March 2022, the Council adopted a decision to authorise the **opening of negotiations** for an international agreement on pandemic prevention, preparedness and response.

The intergovernmental negotiating body, tasked with drafting and negotiating this international instrument, will hold its next meeting by 1 August 2022, **to discuss progress on**

a working draft. It will then deliver a progress report to the 76th World Health Assembly in 2023, with the aim **to adopt the instrument** by 2024.

- › Council gives green light to start negotiations on international pandemic treaty (press release, 3 March 2022)

Why an international pandemic instrument?

Infographic - Towards an international treaty on pandemics



See full infographic

The COVID-19 pandemic is a global challenge. No single government or institution can address the threat of future pandemics alone.

A convention, agreement or other international instrument is **legally binding under international law**. An agreement on pandemic prevention, preparedness and response adopted under the World Health Organization (WHO) would enable countries around the globe to strengthen national, regional and global capacities and resilience to future pandemics.

Such an instrument would also:

- ensure **higher, sustained and long-term political engagement** at the level of world leaders of states or governments
- define **clear processes and tasks**
- enhance **long-term public and private-sector support** at all levels
- foster **integration of health matters across all relevant policy areas**

We need to create an environment where every scientist, health worker, and government can band together for a common cause. Working together to build new solutions to protect what is most precious - our health and our lives.

— Charles Michel, President of the European Council at World Health Summit, 25 October 2021

What's the purpose of an international agreement on pandemics?

The proposal for an international instrument on pandemic prevention, preparedness and response is guided by a spirit of collective solidarity, anchored in the principles of fairness, inclusiveness and transparency.

Neither individual governments nor the global community can entirely prevent pandemics. But the international community needs to be **much better prepared** and **better aligned in responding to possible future pandemics** across the entire cycle of detection, alarm and response.

The instrument would set out the objectives and fundamental principles in order to structure the necessary collective action to fight pandemics.

An international convention, agreement or other international instrument on pandemics would support and focus on:

- **early detection** and **prevention of pandemics**
- **resilience** to future pandemics
- **response** to any future pandemics, in particular by ensuring **universal and equitable access** to medical solutions, such as vaccines, medicines and diagnostics
- a **stronger international health framework** with the WHO as the coordinating authority on global health matters

- the **"One Health" approach**, connecting the health of humans, animals and our planet

More specifically, such an instrument can enhance international cooperation in a number of priority areas, such as surveillance, alerts and response, but also in general trust in the international health system.

Infographic - 10 incentives and benefits of an international treaty on pandemics



See full infographic

What are the main incentives and benefits?

Better surveillance of pandemic risks

The monitoring of risks and, in particular, knowledge-sharing on new infectious diseases spreading from animals to humans is crucial to the prevention of future pandemics.

This could be achieved through:

- increased laboratory and surveillance capacity required to identify animal diseases in all countries
- enhanced collaboration between research centres globally
- better coordination of international funding for core capacities

Better alerts

Introducing more levels of alert commensurate to the degree of health threats would improve accuracy in communication about public health threats. This would enhance the transparency and legitimacy of restrictive or health-related measures.

Digital technologies and innovative tools for data collection and sharing as well as predictive analytics can support real-time communication and early warnings which should, in turn, trigger a more rapid response.

Better response

Health supplies and services

As demonstrated during the COVID-19 pandemic, global supply chains and logistics systems need to be more resilient to cope with global health threats. All countries should have uninterrupted access to essential supplies, medicines and equipment from anywhere in the world.

Global coordination for effective stockpiling may also ease the pandemic response. The ability to deploy medical equipment and highly-skilled international medical teams on the ground would also represent a step forward in global health security.

Research and innovation

The COVID-19 pandemic demonstrated how critical it is for the scientific community to mobilise quickly and for the industry to be able to rapidly scale up their manufacturing capacity.

A globally coordinated approach to discovering, developing and delivering effective and safe medical solutions, such as vaccines, medicines, diagnostics and protective equipment would benefit collective health security.

The sharing of pathogens, biological samples and genomic data as well as the development of timely medical solutions (vaccines, treatments and diagnostics) are vital in order to enhance global pandemic preparedness.

Better response mechanisms

Inequities in access to vaccines, medicines and diagnostics threaten to prolong pandemics and to take a more serious toll on human life and health as well as on our societies and economies.

The agreement would draw the lessons based on the experience of the Access to COVID-19 Tools Accelerator (ACT-A), COVAX and other collective instruments developed since the COVID-19 pandemic started, in order to address global needs more equitably in future pandemics.

Better implementation

The resilience of national public health systems is a crucial element in fighting a pandemic. Countries need to be able to rely on their public health systems in order to effectively respond to the break-out of a pandemic. This could be achieved with a more robust country-reporting mechanism, as well as through the more widespread use of joint external evaluations and better follow-up.

Restoring trust in the international health system

The agreement would ensure that there is more transparency, more accountability, and more shared responsibility in the international system.

In addition, it will set the foundation for better communication and information to citizens. Misinformation threatens public trust and risks undermining public health responses. To redeem citizen trust, concrete measures should be foreseen to improve the flow of reliable and accurate information as well as to tackle misinformation globally.

In the Council

The World Health Organization

The World Health Organization (WHO) was founded in 1948 with the mandate to act as the directing and coordinating authority on international health work. It has 194 member states, across six regions, and more than 150 offices, and works to achieve better health for everyone, everywhere.

› About the WHO (WHO website)

The Council adopted on 20 May 2021 a decision to support the launch of negotiations for an international agreement on the fight against pandemics within the framework of

WHO.

- EU supports start of WHO process for the establishment of Pandemic Treaty: Council decision (press release, 20 May 2021)

The Council adopted on **3 March 2022**, a decision to authorise the opening of negotiations for an international agreement on pandemic prevention, preparedness and response.

The Commission, for matters falling within Union competence, will negotiate the agreement on behalf of the EU, based on the Council's negotiating directives.

Such an instrument would support international efforts to reinforce global health security, in particular on preparedness and response to health emergencies, in light of lessons learnt from the pandemic.

The intergovernmental negotiating body will hold its next meeting by **1 August 2022**, to discuss progress on a working draft. It will then deliver a progress report to the 76th World Health Assembly in 2023, with the aim to adopt the instrument by 2024.

- Council gives green light to start negotiations on international pandemic treaty (press release, 3 March 2022)

During the European Council on 25 March, EU leaders discussed the agreement on pandemic prevention, preparedness and response to be adopted under the World Health Organization (WHO).

- European Council, 24-25 March 2022

Background

The proposal for an international treaty on pandemics was first announced by the President of the European Council, Charles Michel, at the Paris Peace Forum in November 2020.



We need to go further and learn the lessons of the pandemic. We see that it is absolutely crucial to be able to act more quickly and in a more coordinated way, to ensure that medical equipment is available and to exchange information with each other very quickly in order to protect our citizens as best we can.

— Charles Michel, President of the European Council, at the Paris Peace Forum on 12 November 2020

This call for an international treaty on pandemics was also highlighted by the G7 leaders in their statement on 19 February 2021.

› G7 Leaders statement, 19 February 2021

EU leaders agreed to work on an international treaty on pandemics on 25 February 2021.

We are committed to advancing global health security, including by strengthening the World Health Organization and working towards an international treaty on pandemics within its framework.

— Statement of the members of the European Council, 25 February 2021

- › Statement of the members of the European Council on COVID-19 and health, 25 February 2021

At the World Health Assembly, the 194 members of the WHO have adopted on 31 May 2021 the decision to **discuss a new international treaty on pandemics at a special session starting on 29 November 2021**.

- › Report of the WHO working group for the Special Session of the World Health Assembly (World Health Organization)

On 1 December 2021, the 194 members of the World Health Organization (WHO) reached consensus to **kickstart the process to draft and negotiate a convention, agreement or other international instrument** under the Constitution of the World Health Organization to strengthen pandemic prevention, preparedness and response.

An intergovernmental negotiating body will now be constituted and hold its first meeting by 1 March 2022 (to agree on ways of working and timelines) and its second by 1 August 2022 (to discuss progress on a working draft). It will then deliver a progress report to the 76th World Health Assembly in 2023, with the aim to adopt the instrument by 2024.



Dr. Tedros Adhanom Ghebreyesus and Charles Michel championed the idea of an international treaty on pandemics

World leaders call for new international treaty to improve pandemic response

Topics:

On 30 March 2021, leaders from all around the world joined the President of the European Council, Charles Michel and the Director-General of the World Health Organization, Dr. Tedros Adhanom Ghebreyesus in an open call for an international treaty on pandemics, drawing from the lessons learnt during the COVID-19 pandemic.

Share

There will be other pandemics and other major health emergencies. The question is not if, but when. Together, we must be better prepared to predict, prevent, detect, assess and effectively respond to pandemics in a highly coordinated fashion. To that end, we believe that nations should work together towards a new international treaty for pandemic preparedness and response.

— Joint call for an international pandemic treaty

- "COVID-19 shows why united action is needed for more robust international health architecture" op-ed article (press release, 30 March 2021)

Vaccine Timeline

Historic Dates and Events Related to Vaccines and Immunization

It was not too many years ago when we celebrated the 200th anniversary of Edward Jenner's first smallpox vaccination in 1796. The development of vaccines continued at a fairly slow rate until the last several decades when new scientific discoveries and technologies led to rapid advances in virology, molecular biology, and vaccinology. The chart which follows displays many of the vaccine- and immunization-related events that have occurred since Jenner's critical discovery. This list is by no means exhaustive. If you know of an event that you would like us to add, contact us at admin@immunize.org.

Date	Event and related notes
April 1, 2022	ACIP recommends universal HepB vaccination in adults aged 19-59 years.
March 29, 2022	FDA authorizes and CDC recommends second boosters for certain individuals.
March 29, 2022	FDA amends EUA, authorizes additional presentation of Moderna COVID-19 vaccine for booster vaccination doses, (dark blue caps with purple border labels.)
March 18, 2022	ACIP recommends use of Moderna COVID-19 vaccine in adults aged 18 years and older, considerations for extended intervals for primary series doses of mRNA COVID-19 vaccines.
February 22, 2022	ACIP recommends two additional groups for use of Ebola vaccine.
February 18, 2022	CDC released the 2022 recommended immunization schedules for children and adolescents, as well as for adults on its website.
January 31, 2022	FDA approves COVID-19 vaccine Spikevax (Moderna) for individuals 18 years and older. (The EUA remains in effect for third primary series dose and booster dose.)
January 28, 2022	CDC published ACIP updated recommendations for adults on use PCV15 and PCV20.
January 21, 2022	CDC published ACIP Recommendations for use of recombinant zoster vaccine in immunocompromised adults.
January 21, 2022	CDC published ACIP updated interim recommendations for use of the Janssen (Johnson & Johnson) COVID-19 vaccine.
January 7, 2022	FDA shortens interval to booster dose of Moderna COVID-19 vaccine to 5 months.
January 5, 2022	CDC endorses ACIP recommendation to expand eligibility of booster doses to those 12 to 15 years old. CDC recommends that all adolescents 12 to 17 years old should receive a booster shot 5 months after their initial Pfizer-BioNTech vaccination series.
January 4, 2022	CDC recommends Pfizer-BioNTech booster 5 months after completing primary series. CDC recommends moderately or severely immunocompromised 5–11-year-olds receive an additional primary dose of Pfizer-BioNTech COVID-19 vaccine 28 days after their second shot.
January 3, 2022	FDA amends EUA Pfizer-BioNTech vaccine - expands use of a single booster dose to include 12 through 15 years of age, shortens time to booster dose to at least 5 months, and allows for third primary dose for certain immunocompromised children 5 through 11 years of age.
December 17, 2021	CDC published ACIP recommendations on the use of dengue vaccine
December 14, 2021	FDA revises Janssen Fact Sheets to include contraindication and risks of TTS
December 9, 2021	FDA and CDC expand Pfizer-BioNTech booster recommendations to 16 and 17 years of age
November 30, 2021	FDA approves PreHevbrio (VBI Vaccines) for adults 18 years and older
November 29, 2021	CDC recommends all 18 years and older get a COVID-19 booster
November 19, 2021	FDA amends EUAs for COVID-19 mRNA vaccines for use of booster dose for 18 years and older
November 5, 2021	CDC published ACIP Interim Recommendations for use of Pfizer-BioNTech COVID-19 vaccine in children aged 5-11 years
October 29, 2021	FDA authorizes EUA for Pfizer-BioNTech COVID-19 vaccine for children 5-11 years
October 29, 2021	CDC published ACIP Recommendations for COVID-19 additional primary and booster doses

October 20, 2021	FDA amends EUAs of all COVID-19 vaccines, allows for booster doses, and mix and match of doses in eligible individuals
October 14, 2021	FDA approves expanded age indication for Flucelvax Quad (Seqirus), licensed for 6 months and older
September 22, 2021	FDA authorizes booster dose of Pfizer-BioNTech COVID-19 Vaccine for aged 65 years and older, aged 18 through 64 at high risk of severe COVID-19, aged 18 through 64 who have institutional or occupational exposure to SARS-CoV-2
August 27, 2021	CDC released ACIP recommendations on use of influenza vaccines for the 2021–22 influenza season
August 23, 2021	FDA approves first COVID-19 vaccine Comirnaty (Pfizer-BioNTech) for individuals 16 and older. (The EUA remains in effect for individuals 12 years of age and older and for third dose for immunocompromised individuals 12 years of age and older).
August 13, 2021	FDA approves Ticovac (Pfizer) a vaccine to prevent tick-borne encephalitis (TBE) vaccine in individuals 1 year of age and older.
August 12, 2021	FDA amends the emergency use authorizations (EUAs) for Pfizer-BioNTech and Moderna COVID-19 vaccines to allow for use of additional dose in certain immunocompromised individuals.
July 23, 2021	FDA expands indication of Shingrix vaccine to include adults aged 18 years and older who are or will be at increased risk of zoster due to immunodeficiency or immunosuppression caused by known disease or therapy.
July 16, 2021	FDA approves Vaxneuvance (Merck & Co, Inc.) pneumococcal 15-valent conjugate vaccine for adults 18 years or older.
July 8, 2021	FDA revises fact sheets for Janssen COVID-19 Vaccine (Johnson & Johnson), adding Guillain-Barré syndrome (GBS) warning and revising thrombocytopenia warning.
July 6, 2021	Update from ACIP: Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients.
June 25, 2021	FDA revised EUA mRNA (Pfizer and Moderna) patient and provider fact sheets regarding the suggested increased risks of myocarditis and pericarditis following vaccination.
June 9, 2021	FDA approves Prevnar 20 (Pfizer) pneumococcal 20-valent conjugate vaccine for adults 18 years or older
May 14, 2021	ACIP Interim Recommendations for use of Pfizer-BioNTech COVID-19 Vaccine in Adolescents Aged 12–15 years.
May 10, 2021	FDA expands the emergency use authorization of Pfizer-BioNTech COVID-19 vaccine to include adolescents 12–15 years of age.
April 27, 2021	Updated Recommendation from ACIP for Use of Janssen (Johnson & Johnson) COVID-19 Vaccine After Reports of Thrombosis with Thrombocytopenia Syndrome Among Vaccine Recipients
April 23, 2021	CDC and FDA lift recommended pause of use of Johnson & Johnson (Janssen) COVID-19 Vaccine in the U.S. after a review by ACIP. Use of vaccine should resume. EUA fact sheets for Johnson & Johnson (Janssen) COVID-19 Vaccine revised.
April 13, 2021	CDC and FDA recommended a pause in use of the Janssen (Johnson & Johnson) COVID-19 vaccine in the United States out of an abundance of caution. A CDC Health Alert Network (HAN) was issued with recommendations.
March 2, 2021	CDC published ACIP interim recommendations for the use of Janssen (Johnson and Johnson) COVID-19 vaccine.
February 27, 2021	FDA issues Emergency Use Authorization (EUA) for Janssen (Johnson and Johnson) COVID-19 vaccine.
February 12, 2021	CDC released the 2021 recommended immunization schedules for children and adolescents, as well as for adults on its website.
January 8, 2021	CDC published ACIP recommendation on the use of Ebola vaccine.
December 20, 2020	CDC published ACIP interim recommendations for the use of Moderna COVID-19 vaccine.
December 18, 2020	FDA issues Emergency Use Authorization (EUA) for Moderna COVID-19 vaccine.
December 13, 2020	CDC published ACIP interim recommendations for the use of Pfizer-BioNTech COVID-19 vaccine.
December 11, 2020	FDA issues Emergency Use Authorization (EUA) for Pfizer-BioNTech COVID-19 vaccine.
September 25, 2020	CDC published ACIP recommendations on the use meningococcal vaccines.
August 21, 2020	CDC released ACIP recommendations on the use of influenza vaccines for the 2020-2021 influenza season.
July 3, 2020	CDC published updated ACIP recommendations on the use of hepatitis A vaccine.

June 24, 2020	FDA expands license for Gardasil 9 to include preventing oropharyngeal and other head-and-neck cancers caused by relevant HPV types.
April 23, 2020	FDA approves MenQuadfi (MenACWY) conjugate vaccine for prevention of invasive meningococcal disease caused by serogroups A, C, W, and Y in individuals 2 years of age and older.
February 21, 2020	FDA approved Fluvad Quadrivalent (influenza vaccine, adjuvanted; Seqirus) for adults 65 years and older.
February 3, 2020	CDC released the 2020 recommended immunization schedules for children and adolescents, as well as for adults on its website.
February 1, 2020	CDC (January 30, 2020) and WHO (February 1, 2020) declared public health emergencies regarding 2019 novel coronavirus.
January 24, 2020	CDC published updated ACIP recommendations on the use of Td and Tdap vaccines.
December 19, 2019	FDA approved Ervebo (Ebola Zaire vaccine, live; Merck) first U.S.-licensed vaccine for prevention of Ebola virus disease.
December 13, 2019	CDC published ACIP recommendations on the use of BioThrax (anthrax vaccine, adsorbed; Emergent BioSolutions).
November 22, 2019	CDC published updated ACIP recommendations for the use of PCV13 and PPSV23 pneumococcal vaccines for adults age 65 and older.
November 4, 2019	FDA approved Fluzone High-Dose Quadrivalent (Sanofi Pasteur) for adults 65+ years of age—will be available for 2020–21 flu season.
August 28, 2019	CDC released ACIP recommendations on the use of influenza vaccines for the 2019–20 influenza season.
August 16, 2019	CDC published updated ACIP recommendations for human papillomavirus vaccination of adults.
August 1, 2019	AAFP, AAP, ACHA, ACOG, APhA, SAHM, and IAC released "Dear Colleague" letter stressing importance of 16-year-old immunization visit.
July 19, 2019	CDC published ACIP recommendations on use of Japanese encephalitis vaccine.
February 15, 2019	CDC published ACIP recommendations for use of hepatitis A vaccine for persons experiencing homelessness.
February 5, 2019	CDC released the 2019 U.S. recommended immunization schedules for children/adolescents as well as for adults on its website.
January 23, 2019	FDA approved use of the 0.5 mL dose of Sanofi's Fluzone Quadrivalent influenza vaccine to include children age 6 through 35 months.
January 14, 2019	FDA approved expanded use of Sanofi's Adacel Tdap vaccine for a second dose in people ages 10 through 64 years of age.
December 21, 2018	FDA approved Vaxelis (MCM Vaccine Co), a new combination DTaP-IPV-Hib-HepB vaccine for use in children 6 wks–4 yrs of age.
November 7, 2018	ACIP published updated recommendations on use of hepatitis A vaccine for pre- and post-exposure prophylaxis for international travel.
October 25, 2018	The American Dental Association adopted a policy to support the use and administration of HPV vaccine for the prevention of oral HPV infection.
October 8, 2018	FDA approved expanded age indication for Seqirus's Afluria influenza vaccine to include children age 6 months through 59 months.
October 5, 2018	FDA announced approval of expanded use of Merck's Gardasil 9 (HPV9, Human papillomavirus) vaccine to include adults 27 through 45 years old.
August 24, 2018	CDC published ACIP's 2018–19 influenza vaccination recommendations.
June 8, 2018	CDC published ACIP's recommendations for the use of quadrivalent live attenuated influenza vaccine (LAIV4) in the 2018–19 influenza season.
June 2018	The American College of Obstetricians and Gynecologists issued a committee opinion on maternal immunization.
May 16, 2018	CDC released information about a new rapid rabies test that could save lives and lead to fewer unnecessary rabies shots.
April 27, 2018	CDC published a comprehensive summary of previously published ACIP recommendations for prevention of tetanus, diphtheria, and pertussis in the U.S.
April 20, 2018	CDC published ACIP recommendations for use of hepatitis B vaccine with a novel adjuvant [HepBisav-B].
April 2018	The American College of Obstetricians and Gynecologists released a committee opinion on influenza vaccination in pregnancy.
February 6, 2018	CDC published the 2018 U.S. recommended immunization schedule for 0 through 18 years.
February 6, 2018	CDC published the 2018 U.S. recommended adult immunization schedule.

January 26, 2018	CDC published ACIP recommendations for use of herpes zoster vaccines.
January 12, 2018	CDC published updated ACIP recommendations for prevention of hepatitis B virus infection.
January 12, 2018	CDC published ACIP recommendations on use of a third dose of MMR during a mumps outbreak.
January 11, 2018	FDA approved expanded pediatric age indication for Fluarix Quadrivalent influenza vaccine.
November 9, 2017	FDA licensed HepHisav-B, the new hepatitis B vaccine from Dynavax, for use in adults age 18 and older.
October 20, 2017	FDA licensed Shingrix, the new shingles vaccine from GlaxoSmithKline, for use in adults age 50 and older.
September 15, 2017	CDC published updated dosing instructions for hepatitis A prophylaxis with immune globulin.
August 31, 2017	FDA expanded licensure of Afluria quadrivalent (Seqirus) to include people age 5 years and older.
August 25, 2017	CDC published ACIP 2017–18 influenza vaccination recommendations.
August 2017	AAP issued policy stating that newborns should routinely receive hepatitis B vaccine within 24 hours of birth.
July 6, 2017	CDC published a Vaccine Information Statement for cholera.
June 30, 2017	CDC and FDA announced new Vaccine Adverse Event Reporting website and reporting form.
May 19, 2017	CDC published ACIP's updated recommendations on use of Trumenba meningococcal serogroup B vaccine.
May 12, 2017	CDC published ACIP recommendations for use of cholera vaccine.
April 20, 2017	CDC published ACIP recommendations titled "General Best Practice Guidelines for Immunization" to replace the 2011 "General Recommendations on Immunization."
February 7, 2017	CDC published the 2017 U.S. recommended immunization schedules for 0 through 18 years; includes new "16-year-old vaccination" column.
February 7, 2017	CDC published the 2017 U.S. recommended adult immunization schedule.
December 16, 2016	CDC published ACIP's recommendations on 2-dose HPV vaccine series for younger adolescents.
November 18, 2016	FDA approved extending the age range for use of FluLaval Quadrivalent to include children 6 to 35 months of age.
November 4, 2016	CDC published ACIP recommendations for use of meningococcal conjugate vaccines in HIV-infected persons.
September 27, 2016	PAHO/WHO announced measles elimination in the Americas.
August 26, 2016	CDC published 2016–17 influenza vaccination recommendations.
August 2016	AAP released new policy statement that urges states to eliminate all non-medical exemptions to vaccine requirements.
July 11, 2016	FDA extended the age indication for PCV13 (Prevnar 13) to include adults age 18 through 49 years.
June 22, 2016	ACIP voted that live attenuated influenza vaccine (LAIV) should not be used during the 2016–2017 flu season.
June 15, 2016	FDA approved revisions in the package insert for YF-Vax to reflect changes to International Health Regulations and WHO/ACIP recommendations.
June 10, 2016	FDA approved Vaxchora for the prevention of cholera.
April 14, 2016	FDA approved changes to vaccine administration schedule for Trumenba vaccine.
February 5, 2016	National Vaccine Program Office released an National Adult Immunization Plan.
February 1, 2016	2016 U.S. recommended immunization schedules for 0 through 18 years and "catch up" published in <i>MMWR</i> .
January 14, 2016	FDA approved Hiberix for full Hib vaccine series.
December 14, 2015	FDA expanded Gardasil 9 licensure to include males age 16–26 years.
November 24, 2015	FDA approved new injectable influenza vaccine, Fluad, for use in people age 65 years and older
October 23, 2015	ACIP published recommendations for the use of serogroup B meningococcal vaccines in adolescents and young adults.
September 4, 2015	CDC published updated ACIP recommendations regarding the intervals between PCV13 and PPSV23 vaccines for use in immunocompetent adults age 65 years and older

August 14, 2015	WHO published "Recommendations on Vaccine Hesitancy" in special issue of the journal <i>Vaccine</i> .
June 19, 2015	ACIP published recommendations for yellow fever booster doses.
June 12, 2015	ACIP published recommendations for use of serogroup B meningococcal vaccines in people age ten years and older at increased risk for serogroup B meningococcal disease.
June 8, 2015	American Medical Association adopted a new policy that supports ending non-medical vaccine exemptions, including those for healthcare professionals.
April 29, 2015	The Pan American Health Organization declared rubella eliminated in the Americas.
March 27, 2015	CDC published ACIP recommendations for use of 9-valent HPV vaccine.
March 27, 2015	CDC published new ACIP recommendations for typhoid vaccination.
March 24, 2015	FDA approved Quadracel, a new combination DTaP+IPV vaccine for use in children age 4–6 years.
January 23, 2015	CDC's Health Alert Network issued a health advisory about a multi-state outbreak of measles linked to Disneyland.
January 23, 2015	FDA approved the use of Bexsero, the second vaccine licensed in the U.S. to prevent serogroup B meningococcal disease.
December 19, 2014	FDA approved Rapivab to treat influenza infection.
December 11, 2014	FDA approved quadrivalent formulation of Fluzone Intradermal inactivated influenza vaccine.
December 10, 2014	FDA approved the use of Gardasil 9 (Merck) 9-valent HPV vaccine in the U.S.
October 29, 2014	FDA approved the use of Trumenba in the U.S. to prevent serogroup B meningococcal disease.
September 19, 2014	CDC published ACIP recommendations for use of PCV13 and PPSV23 vaccines in adults age 65 and older.
June 20, 2014	CDC published ACIP's recommendations for use of MenACWY-CRM vaccine in children age 2–23 months at increased risk for meningococcal disease.
May 5, 2014	WHO Director-General declared the international spread of wild poliovirus in 2014 a Public Health Emergency of International Concern.
April 25, 2014	CDC report showed 20-year U.S. immunization program spares millions of children from diseases.
March 24, 2014	FDA lowered age of licensure for Adacel vaccine administration from age 11 years to 10 years.
February 28, 2014	CDC published ACIP recommendations for prevention and control of Haemophilus influenzae type b (Hib) disease.
December 20, 2013	CDC published guidance for HBV protection and postexposure management of healthcare personnel.
November 15, 2013	CDC published new recommendations for use of Japanese encephalitis vaccine in children.
September 10, 2013	National Vaccine Advisory Committee released revised "Standards for Adult Immunization Practice."
August 16, 2013	FDA extended FluLaval IIV (GlaxoSmithKline) age range to include children and teens age 3–17 years; licenses quadrivalent FluLaval product.
August 1, 2013	FDA expanded age indication for Menveo (Novartis) to include infants and toddlers age 2 through 23 months.
July 19, 2013	CDC issued updated recommendations for use of VarizIG immune globulin for varicella postexposure prophylaxis.
June 28, 2013	CDC issued recommendations for PCV and PPSV vaccination of children with immunocompromising conditions.
June 20, 2013	ACIP voted to recommend FluBlok influenza vaccine for people age 18 through 49 with egg allergy.
June 14, 2013	CDC published recommendations for preventing measles, rubella, congenital rubella syndrome, and mumps.
June 7, 2013	FDA approved Fluzone (Sanofi Pasteur) as the third quadrivalent influenza vaccine licensed for U.S. use.
May 17, 2013	Booster dose of yellow fever vaccine not needed, according to WHO. A single dose of vaccine is effective in providing long-term protection from yellow fever.
February 22, 2013	ACIP recommended a dose of Tdap vaccine during each pregnancy.
February 8, 2013	UNICEF and WHO condemned attacks on polio vaccination workers in Nigeria.
January 25, 2013	FDA approved use of Prevnar 13 vaccine in older children and teens (6-17 years).

December 18, 2012	Institute for Safe Medication Practices (ISMP) launched new Vaccine Error Reporting Program.
December 12, 2012	FDA approved quadrivalent formulation of Fluarix (inactivated influenza vaccine; GlaxoSmithKline).
November 20, 2012	FDA approved first seasonal influenza vaccine manufactured using cell culture technology (Flucelvax, Novartis).
October 24, 2012	ACIP voted to recommend use of HibMenCY (Menhibrix, GlaxoSmithKline), a new combination (meningococcal and Hib) vaccine, in infants at increased risk for meningococcal disease.
October 24, 2012	ACIP voted to recommend that pregnant women receive a dose of Tdap during each pregnancy irrespective of the patient's prior history of receiving Tdap.
June 24, 2012	FDA approved HibMenCY (Menhibrix, GlaxoSmithKline), a new combination (meningococcal and Hib) vaccine for infants.
June 7, 2012	FDA expanded licensure of PCV13 to include adults ages 50 years and older.
June 5, 2012	U.S. Department of Health and Human Services (HHS) Office of the Inspector General (OIG) released a report titled "Vaccines for Children (VFC) Program: Vulnerabilities in Vaccine Management."
April 1, 2012	United Nations Foundation launched Shot@Life campaign.
December 30, 2011	FDA expanded use of Prevnar 13 (PCV13, Pfizer) vaccine to include people ages 50 and older.
October 25, 2011	ACIP recommended all 11 to 12 year-old males get vaccinated against HPV.
October 21, 2011	Addition of history of intussusception as a contraindication for rotavirus vaccination.
August 25, 2011	National survey indicated HPV vaccine rates trail other teen vaccines.
August 25, 2011	Institute of Medicine issued the report titled "Review of Adverse Effects of Vaccines." Overall, the committee concludes that few health problems are caused by or clearly associated with vaccines.
July 8, 2011	FDA approved Boostrix (Tdap, GlaxoSmithKline) to prevent tetanus, diphtheria, and pertussis in older people.
May 19, 2011	CDC hailed vaccinations as one of 10 public health achievements of first decade of 21st century in Morbidity and Mortality Weekly Report (MMWR).
April 22, 2011	FDA approved the first vaccine (Menactra, meningococcal conjugate vaccine, Sanofi Pasteur) to prevent meningococcal disease in infants and toddlers.
February 15, 2011	HHS releases U.S. National Vaccine Plan, covers activities, goals, and priorities for 2010-2015.
December 22, 2010	FDA approved Gardasil HPV vaccine to include the indication for the prevention of anal cancer.
August 11, 2010	WHO declared end to 2009 H1N1 influenza pandemic.
July 10, 2010	First smallpox vaccine for certain immune-compromised populations delivered under Project BioShield.
March 19, 2010	ACIP recommended use of a reduced (4-dose) vaccine schedule for PEP to prevent human rabies.
February 24, 2010	FDA approved licensure of Pneumococcal 13-valent conjugate vaccine (PCV13), which offers broader protections against <i>Streptococcus pneumoniae</i> infections.
February 19, 2010	FDA approved licensure of Menveo (Novartis), meningococcal conjugate vaccine for people ages 11 through 55 years.
January 29, 2010	WHO hailed new Gates Foundation support (\$10 billion) as the "Decade of Vaccines."
February 24, 2010	ACIP recommended universal Influenza vaccination for those 6 months of age and older.
February 24, 2010	FDA approved pneumococcal 13-valent conjugate vaccine (Prevnar 13), which offers broader protection against <i>Streptococcus pneumoniae</i> .
December 23, 2009	FDA approved high-dose inactivated influenza vaccine (Fluzone High-Dose) for people ages 65 years and older.
November 16, 2009	CDC issued Health Advisory 2009 H1N1 Pandemic Update: Pneumococcal vaccination recommended to help prevent secondary infections.
October 21, 2009	Merck issued announcement that the company will not resume production of monovalent measles, mumps, and rubella vaccines.
October 16, 2009	FDA approved new vaccine (Cervarix, GlaxoSmithKline) for the prevention of cervical cancer.
October 16, 2009	FDA approved new indication for gardasil to prevent genital warts in men and boys.
September 15, 2009	FDA approved four vaccines against the 2009 H1N1 influenza virus.

July 1, 2009	WHO and ACIP issued recommendations on the use of H1N1 influenza vaccines.
June 23, 2009	HHS announced advanced development contract for new way to make flu vaccine.
June 11, 2009	Dr Margaret Chan, Director-General WHO, declared world now at the start of 2009 influenza pandemic.
May 22, 2009	HHS directed \$1 billion toward development of vaccine for novel influenza A (H1N1).
March 16, 2009	ACIP voted to recommend hepatitis A vaccination for close contacts of international adoptees from countries with high and intermediate endemicity.
February 12, 2009	Vaccine Court ruled that MMR vaccine, when administered with thimerosal-containing vaccines, does not cause autism.
January 15, 2009	HHS awarded a \$487 million contract to Novartis Vaccines and Diagnostics, Inc to build a facility to manufacture cell-based influenza vaccine.
December 11, 2008	FDA approved changes in the schedule for administering anthrax vaccine (BioThrax, manufactured by Emergent BioSolutions) and in the route of administration.
December 4, 2008	FDA approved expanded indication for use of Boostrix Tdap vaccine in people ages 10-64 years.
October 27, 2008	National Quality Forum included the hepatitis B birth dose among its consensus standards for improving health care for mothers and newborns.
June 24, 2008	FDA approved new DTaP-IPV vaccine (Kinrix) for use in children ages 4-6 years.
June 20, 2008	FDA approved Pentacel (Sanofi Pasteur), a new combination DTaP-IPV-Hib vaccine for use in children 6 wks–4 yrs of age.
June 5, 2008	FDA approved the use of Sanofi Pasteur's Tenivac tetanus and diphtheria toxoids adsorbed for adults age 60 years and older. In the original licensure, the age indication was for persons ages 7-59 years.
April 3, 2008	FDA approved new rotavirus vaccine (Rotarix) for use in U.S. Rotarix is a liquid and given in a two-dose series to infants from 6 to 24 weeks of age.
April 2, 2008	CDC issued Health Advisory in response to widespread measles outbreaks in U.S.
March 14, 2008	CDC updated its recommendations for administering combination MMRV vaccine.
February 29, 2008	CDC announced it had begun distribution of a new-generation smallpox vaccine, ACAM2000 (Acambis, Inc., Cambridge, Massachusetts), to civilian laboratory personnel, the military, and state public health preparedness programs.
February 27, 2008	ACIP voted to expand influenza recommendation to include vaccination for children ages 6 months-18 years.
December 7, 2007	CDC published updated recommendation for meningococcal vaccination of at-risk children age 2-10 years in MMWR.
October 26, 2007	ACIP voted to recommend the use of FluMist, the live attenuated influenza vaccine (LAIV; nasal-spray formulation) to include children age 2-5 years.
October 19, 2007	CDC published updated recommendations for prevention of hepatitis A virus infection after exposure and before international travel in MMWR.
October 18, 2007	FDA approved use of Menactra, a bacterial meningitis vaccine, in children age 2-10 years.
September 28, 2007	FDA approved Afluria, a new inactivated influenza vaccine for use in people age 18 years and older.
September 19, 2007	FDA approved use of FluMist nasal-spray influenza vaccine in children age 2-5 years.
August 10, 2007	CDC notified MMWR readers of revised recommendations to vaccinate all persons ages 11-18 with MCV4 at earliest opportunity.
July 20, 2007	MMWR notified readers that revised International Health Regulations have gone into effect for the United States.
July 17, 2007	HHS announced a plan to provide \$175 million to assist states in pandemic influenza preparedness efforts.
June 27-28, 2007	ACIP voted to recommend routine use of meningococcal conjugate vaccine in adolescents ages 11-18 years.
June 15, 2007	HHS awarded \$132.5 million to Sanofi Pasteur and MedImmune over five years to retrofit existing domestic vaccine manufacturing facilities on a cost-sharing basis and to provide warm-base operations for manufacturing pandemic influenza vaccines.
March 28, 2007	FDA approved an accelerated dosing schedule for Twinrix (hepatitis A and B vaccine). The schedule consists of three doses given within three weeks followed by a booster dose at 12 months (0, 7, 21–30 days, 12 months).
April 17, 2007	FDA approves first U.S. vaccine for humans against the avian influenza virus H5N1.

January 7, 2007	FDA licensed the refrigerator formulation of FluMist.
June 29, 2006	ACIP recommends second dose of varicella vaccine for children.
June 8, 2006	FDA licensed the first vaccine developed to prevent cervical cancer (Gardasil by Merck & Co., Inc.), precancerous genital lesions, and genital warts due to human papillomavirus (HPV) types 6, 11, 16, and 18.
May 25, 2006	FDA licensed a new vaccine to reduce the risk of shingles (herpes zoster) in the elderly. The vaccine (Zostavax by Merck & Co., Inc.) is approved for use in people aged 60 years of age and older.
Feb 24, 2006	VariZIG, a new immune globulin product for postexposure prophylaxis of varicella, is available under an Investigational New Drug Application Expanded Access Protocol.
Feb 3, 2006	Rotavirus vaccine, live, oral, pentavalent (RotaTeq by Merck) was licensed for use in infants ages 6 to 32 weeks.
Dec 19, 2005	A final order on the anthrax vaccine was issued by FDA, stating that the licensed anthrax vaccine is safe and effective for the prevention of anthrax disease, regardless of the route of exposure.
Oct 18, 2005	FDA approved lowering the age limit to 12 mos for the remaining U.S.-licensed hepatitis A vaccine in the U.S. (Havrix by GlaxoSmithKline).
Oct 7, 2005	A new Federal Medicare rule became effective that required all long-term care facilities to offer annual vaccination for influenza and one-time vaccination for pneumococcal disease to all residents as a condition of participation in Medicare.
Sept 6, 2005	A vaccine that combined the measles, mumps, rubella, and varicella antigens (Proquad by Merck) was licensed. The vaccine was indicated for use in children 12 months to 12 years.
Aug 31, 2005	An inactivated, injectable influenza vaccine (Fluarix by GlaxoSmithKline) was licensed. The vaccine was indicated for adults 18 years of age and older.
Aug 11, 2005	FDA approved lowering the age limit to 12 mos for one of the two licensed hepatitis A vaccine (Vaqta by Merck).
June 10, 2005	FDA licensed a 2nd Tdap vaccine (Adacel by Sanofi Pasteur) for use in persons ages 11-64 years.
May 3, 2005	An acellular pertussis vaccine combined with the adult formulation of tetanus and diphtheria (Tdap: Boostrix by GSK) was licensed for use as an active booster in persons 10-18 years of age. This product became the first licensed acellular pertussis-containing vaccine with an indication for adolescents.
April 3, 2005	DHHS awarded a contract for \$97 million to Sanofi Pasteur to develop cell culture-based influenza vaccines for the U.S.
March 21, 2005	CDC announced that rubella was no longer endemic in the U.S.
Jan 14, 2005	The first meningococcal polysaccharide (Serogroups A, C, Y and W-135) diphtheria toxoid conjugate vaccine (Menactra by Sanofi Pasteur) was licensed. This marked the first meningococcal vaccine that was immunogenic and indicated for children younger than 2 years of age.
Aug - Oct, 2004	A significant shortage of influenza vaccine occurred in the U.S. (History: On August 25, 2004, as a result of routine testing required by FDA, Chiron Corporation, located in the U.K. and one of two suppliers of inactivated influenza vaccine for the U.S., identified bacterial contamination in a limited number of lots (approx 4.5 million doses) of its influenza vaccine. Chiron was expected to produce between 46 and 48 million doses of vaccine for the U.S. as part of a total vaccine supply of about 100 million doses. On Oct 4, 2004, authorities in the U.K. suspended the company's license for 3 months. On Oct 16, 2004, FDA announced that none of the influenza vaccine manufactured by Chiron for the U.S. market was safe for use. U.S. authorities recommended allocation of vaccine to those at highest risk of complications from influenza.)
May 4, 2004	The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institute of Health (NIH), awarded a new license agreement for RotaShield, an oral rotavirus vaccine, created by NIAID scientists in the 1980s. The licensed was awarded to BIOVIRx, Inc., of Minneapolis, MN, which planned global commercialization of RotaShield.
May 2004	Contracts were awarded to Aventis Pasteur and to Chiron to develop vaccine against the H5N1 avian influenza virus.
2004	The 8th and final report of the Immunization Safety Review Committee was issued by the Institute of Medicine. The report concluded that the body of epidemiological evidence favors rejection of a causal relationship between the MMR vaccine (and thimerosal-containing vaccines) and autism.
March 24, 2004	Tetanus and diphtheria toxoids adsorbed for adult use (Decavac by Aventis Pasteur), preservative-free, was licensed.
Oct. 15, 2003	ACIP voted to recommend that children 6 to 23 months of age be vaccinated annually against influenza, with implementation scheduled for the fall of 2004.
2003	\$81 million was awarded by NIAID through four new contracts to support development of candidate HIV vaccines. The awards were part of NIAID's HIV Vaccine Design and Development Teams program, a public-private partnership that seeks to accelerate HIV vaccine development. The contract recipients were

	AlphaVax Human Vaccines, Inc. (Durham, NC), Epimmune, Inc. (San Diego, CA), Novavax, Inc. (Columbia, MD), and Progenics Pharmaceuticals (Tarrytown, NY).
2003	Project Bioshield Act of 2003 was enacted. It authorized more than \$5 billion over 10 years to pay for development of vaccines, drugs, and other biomedical countermeasures for biological, chemical, nuclear, and radiological weapons. The Act also empowered the Secretary of Health and Human Services to authorize the use of drugs and vaccines not licensed by the FDA in the event of an act of bioterrorism or other public health emergencies.
June 17, 2003	The first nasally administered influenza vaccine (FluMist by MedImmune) was licensed. This live influenza A and B virus vaccine was indicated for healthy, non-pregnant persons ages 5-49 years.
Dec 13, 2002	A vaccine that combined the diphtheria, tetanus, acellular pertussis, inactivated polio, and hepatitis B antigens (Pediarix by GlaxoSmithKline) was licensed.
June 21, 2002	The European Region of the world was certified as polio-free.
May 14, 2002	Diphtheria and tetanus toxoids and acellular pertussis vaccine (Daptacel by Aventis Pasteur) was licensed.
Feb 25, 2002	GlaxoSmithKline announced that the company would no longer manufacture or distribute its Lyme disease vaccine, LYMERix, because of insufficient sales of the vaccine.
Dec 13, 2002	President Bush announced a major smallpox vaccination program to protect the nation against the threat of potential biological warfare. The first phase of the program was targeted to 450,000 public health and healthcare personnel, however, the program stalled, with fewer than 40,000 health care workers and emergency responders vaccinated.
2001	The Bill and Melinda Gates Foundation earmarked \$70 million to develop and produce meningitis vaccines tailored for children and adults living in Africa.
2001	Following the events of September 11, 2001, IOM again called for creation of a national vaccine authority ""to advance the development, production, and procurement of new and improved vaccines of limited commercial potential but of global public health need.""
May 11, 2001	A combined hepatitis A inactivated and hepatitis B (recombinant) vaccine (Twinrix by SmithKline Beecham) was licensed.
Feb 17, 2000	A 7-valent pneumococcal conjugate vaccine (Prevnar by Wyeth Pharmaceuticals) was licensed for use in infants at 2, 4, 6 and 12-15 months of age to prevent invasive pneumococcal disease
2000	Measles was declared no longer endemic in the U.S. following eradication campaigns that began in 1967.
2000	The Western Pacific Region of the world was certified as polio-free.
Dec 9, 1999	Diphtheria and tetanus toxoids and acellular pertussis vaccine (Tripedia by Connaught) was licensed.
Oct 22, 1999	ACIP voted to withdraw their recommendation for rotavirus vaccine after investigating reports of intussusception (a type of bowel obstruction that occurs when one part of the intestine folds into an immediately adjoining part) in infants within the first two weeks of receipt of the vaccine. Intussusception was found to occur at a rate of approximately 1 case for every 5,000 children vaccinated.
Oct 16, 1999	Wyeth Lederle Vaccines voluntarily withdrew Rotashield from the market.
Fall 1999	A meningococcal group C conjugate vaccine was introduced into the routine schedule in the U.K. for infants, adolescents (15-17 yrs), and college entrants. A second phase was planned to begin in January 2000, subject to availability of vaccine.
Sept 1999	FDA approved a 2-dose schedule of hepatitis B vaccination for adolescents 11-15 years of age using Recombivax HB (Merck) with the 10 µg (adult) dose at 0 and 4-6 months later.
June 17, 1999	ACIP recommended exclusive use of inactivated poliovirus vaccine (IPV) for infants and children
1999	The Dale and Betty Bumpers Vaccine Research Center (VRC) was established at the National Institutes of Health to facilitate research in vaccine development. The primary focus of VRC research was to be the development of vaccines for AIDS.
1998	ACIP recommended DTaP vaccines for all five doses in the vaccination schedule, because local reactions, fever, and other systemic events were found to occur substantially less often after DTaP administration than after administration of whole cell DTP.
Aug 26, 1998	The Children's Vaccine Program was established at WHO's Program for Appropriate Technology in Health (PATH) with a \$125 million gift from the Bill and Melinda Gates Foundation. The program's goal was to provide vaccines to children in the developing world and to accelerate research and development of new vaccines. The first vaccines purchased were Hib, hepatitis B, rotavirus, and pneumococcal, which were not commonly used in the developing world.
Dec 21, 1998	Lyme Disease Vaccine (Recombinant OspA), (LYMERix by SmithKline Beecham) was licensed for use in persons ages 15 to 70 years. ACIP recommended that decisions on the use of the vaccine be made on the basis of assessment of

	individual risk, which included the extent of both person-tick contact and geographic risk. Just 3+ years later, on February 25, 2002, GlaxoSmithKline announced that the company would no longer manufacture or distribute LYMErix because of insufficient sales of the vaccine.
Aug 31, 1998	Rotavirus vaccine, live, oral, tetravalent (RotaShield by Wyeth) was licensed for use in infants at 2, 4, and 6 months of age.
July 29, 1998	Diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (Certiva by North American Vaccine) was licensed for primary and booster immunization of infants and children (except as a 5th dose in children who have previously received 4 doses of DTaP).
1998	The first vaccine for the prevention of HIV/AIDS (Aidsvax) entered Phase III trial, the first large-scale human trial of an HIV vaccine. The trial involved more than 5,400 volunteers from the U.S., Canada, and the Netherlands, the majority of whom were men who have sex with men. Preliminary results from the trial AIDS VAX (VaxGen) vaccine were reported in early 2003. The HIV vaccine appeared to show a protective effect among non-Caucasian populations, especially African Americans, although sample sizes were small. However, for the majority of the participants, who were Caucasians, the effect of the vaccine was minimal.
Nov 21, 1997	The FDA Modernization Act (FDAMA) was signed into law, amending the Food, Drug and Cosmetic Act and the Public Health Service Act to modernize the regulation of food, medical products, and cosmetics. FDAMA initiatives included measures to modernize the regulation of biological products. Specifically, changes included eliminating the need for establishment license applications, streamlining the approval processes for manufacturing changes, and reducing the need for environmental assessment as part of a product application.
1997	ACIP recommended booster doses of pneumococcal polysaccharide vaccine after 5 years for persons at highest risk of disease.
Oct 20, 1997	Rabies vaccine (RabAvert by Chiron Behring) was licensed.
Jan 29, 1997	Diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (Infanrix by SmithKline Beecham) was licensed for the first four doses of the series.
Jan 1997	ACIP recommended adoption of a sequential series of two doses of IPV followed by two doses of OPV for all infants and children to decrease the rare occurrences of Vaccine Associated Paralytic Polio (VAPP) that were noted following the administration of live oral poliovirus vaccine.
Dec 30, 1996	Diphtheria and tetanus toxoids and acellular pertussis vaccine (Acel-Imune by Lederle) was licensed for use as the first through fifth doses in the series.
Sept 27, 1996	Combination DTaP and Hib vaccine (TriHIBit by Aventis Pasteur) was licensed for the fourth dose in the DTaP and Hib series.
July 31, 1996	Diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (Tripedia by Aventis Pasteur) was licensed for primary and booster immunization of infants.
1996	The International AIDS Vaccine Initiative (IAVI) was launched, calling for the speedy development of a human immunodeficiency virus (HIV) vaccine for use worldwide. The Initiative created the Scientific Blueprint for AIDS Vaccine Development. Since 1996, IAVI invested nearly \$20 million in the research and development of HIV vaccines by companies and research institutes worldwide. IAVI received major financial support from the Bill and Melinda Gates Foundation; the World Bank; the Rockefeller, Sloan and Starr foundations; Becton, Dickinson & Co.; and eight national governments, among other donors. IAVI is a Collaborating Centre of the Joint United Nations Programme on HIV/AIDS (UNAIDS).
Oct 2, 1996	A combined <i>Haemophilus influenzae</i> type b conjugate and hepatitis B vaccine (Comvax by Merck) was licensed.
Mar 29, 1996	A second inactivated hepatitis A vaccine (Vaqta by Merck) was licensed.
Feb 22, 1995	The first inactivated hepatitis A vaccine (Havrix by SmithKline Beecham) was licensed.
Mar 17, 1995	Varicella virus vaccine, live (Varivax by Merck) was licensed for the active immunization of persons 12 months of age and older.
1995	The ACIP, American Academy of Pediatrics, and the American Association of Family Physicians issued the first "harmonized" childhood immunization schedule, combining recommendations of all three national groups.
Nov 28, 1994	Typhoid Vi polysaccharide inactivated injectable polysaccharide vaccine (Typhim Vi by Aventis Pasteur) was licensed.
1994	The Global Programme for Vaccines and Immunization was created, merging two WHO programs -- the Expanded Programme for Immunization and the former Programme for Vaccine Development, and adding a new unit for Vaccine Supply and Quality.
1994	The entire Western Hemisphere was certified as "polio-free" by the International Commission for the Certification of Polio Eradication, WHO.
1993	The Institute of Medicine published "The Children's Vaccine Initiative: Achieving the Vision." Later, following the events of September 11, 2001, the Institute of Medicine again called for creation of a national vaccine authority ""to advance the development, production, and procurement of new and improved vaccines of limited commercial potential but of global public health need.""

1993	The National Immunization Program (NIP) was created as a separate program reporting directly to the Office of the Director at CDC. NIP was established to provide federal leadership and services to all local and state public health departments involved in immunization activities (e.g., disease surveillance for vaccine-preventable diseases, development of vaccine information management systems).
May 1, 1993	The costs of influenza vaccine and its administration became a covered benefit under Medicare Part B.
March 1993	Conjugated <i>Haemophilus influenzae</i> type b vaccines (ActHIB by Connaught/Mérieux and OmniHib by SmithKline Beecham) were licensed.
March 1993	A combined <i>Haemophilus influenzae</i> type b vaccine and whole cell DTP vaccine (Tetramune by Lederle/Praxis) was licensed.
1993	The development of immunization registries was promoted at the national level. A national health goal for 2010 was subsequently established to increase the participation in population-based immunization registries to 95%.
1993	The Vaccines for Children Program was established after passage of the Omnibus Budget Reconciliation Act of 1993. Federally-purchased vaccines under this program were made available to children from birth through 18 years of age who met one of the following requirements: Medicaid-enrolled, without health insurance, and American Indian or Alaskan native. Also, children with health insurance that did not cover the costs of immunization were eligible to receive vaccines at a federally-qualified health center or a rural health clinic. All ACIP recommended vaccines received funding, which included new vaccines, new vaccine combinations, and revised recommendations for vaccine use.
Dec 10, 1992	Japanese encephalitis (JE) virus vaccine inactivated (JE-Vax by Research Foundation for Microbial Diseases of Osaka University [BIKEN]) was licensed. JE is the leading cause of viral encephalitis in Asia. WHO acts as a facilitator for the development of new JE vaccines that are safer, require fewer doses, and are more suitable for public health use, in particular, in disease-endemic developing countries.
Sept 20, 1992	Diphtheria and tetanus toxoids and acellular pertussis vaccine (Tripedia by Connaught) was licensed for use as the fourth and fifth doses in the series.
Dec 17, 1991	Diphtheria and tetanus toxoids and acellular pertussis vaccine (Acel-Imune by Lederle) was licensed for use as the fourth and fifth doses in the series.
Nov 22, 1991	ACIP recommendations for routine hepatitis B vaccination for all infants were published in <i>MMWR</i> .
August 1991	The last case of indigenous polio in the Western Hemisphere occurred in a 5-year-old boy, Luis Fermin Tenorio, in Pichanaqui, Peru.
Jan 11, 1991	Recommendations of ACIP for routine Hib vaccination for infants beginning at 2 months of age were published in <i>MMWR</i> .
Dec 21, 1990	An enhanced-potency inactivated poliovirus vaccine (Ipol by Pasteur Méérieux Vaccins et Serums) was licensed.
April 13, 1990	ACIP recommendations for use of any of the three licensed Hib conjugate vaccines (ProHIBIT, HibTITER, and PedvaxHIB) for children as young as 15 months of age were published in <i>MMWR</i> .
Dec 20, 1989	Conjugated <i>Haemophilus influenzae</i> type b (Hib) vaccine (PedvaxHIB by Merck) was licensed.
Dec 15, 1989	A live, oral typhoid vaccine (Ty21a, <i>Vivotif Berna</i> by Swiss Serum Institute) was licensed.
Aug 28, 1989	Recombinant hepatitis B vaccine (Engerix-B by SmithKline Beecham) was licensed.
1989	Recommendations for routine 2nd doses of measles-containing vaccine were issued by both ACIP and the AAP. During the mid- to late-1980s, a high proportion of reported measles cases were in school-aged children (5-19 years) who had been appropriately vaccinated. These vaccine failures led to national recommendations for a second dose of measles-containing vaccine.
Dec 21, 1988	Conjugated <i>Haemophilus influenzae</i> type b vaccine (HibTITER by Wyeth-Lederle) was licensed.
1988	The Center for Biologics Evaluation and Research (CBER) was created within the FDA to regulate biological products, including blood, vaccines, tissue, allergenics, and biological therapeutics.
1988	The World Health Assembly (the ministers of health of all member states of the WHO) passed a resolution to eradicate polio by the year 2000.
1988	The National Vaccine Injury Compensation Program (NVICP) was established to provide compensation following a vaccine-related adverse event that resulted in injury or death. NVICP was intended to serve as an alternative to civil litigation. The law established a Vaccine Injury Table that provided a list of compensable vaccination events and, for each, an associated time period requirement.
Jan 22, 1988	ACIP recommendations to administer Hib conjugate vaccine to all children at 18 months of age were published in <i>MMWR</i> .
Dec 22, 1987	Protein-conjugated <i>Haemophilus influenzae</i> type b vaccine (PRP-D, ProHibit by Connaught) was licensed.

July 23, 1986	Recombinant hepatitis B vaccine (Recombivax HB by Merck) was licensed. Using recombinant DNA technology, Merck scientists developed a hepatitis B surface antigen subunit vaccine.
1986	Congress created the National Vaccine Program (NVP) to coordinate the vaccine research and development programs of AID, NIH, CDC, the Department of Defense, and FDA.
1986	The National Childhood Vaccine Injury Act of 1986 was enacted by Congress. The Department of Health and Human Services established the Vaccine Adverse Event Reporting System (VAERS), co-administered by FDA and CDC, to accept all reports of suspected adverse events, in all age groups, after the administration of any U.S.-licensed vaccine. The Act required healthcare providers and vaccine manufacturers to report to the Department of Health and Human Services specific adverse events following the administration of measles, mumps, rubella, polio, pertussis, diphtheria, and tetanus vaccine and any combinations thereof.
Apr 12, 1985	<i>Haemophilus influenzae</i> type b (Hib) polysaccharide vaccines (b-CAPSA 1 by Praxis Biologics, Hib-VAX by Connaught, and Hib-IMUNE by Lederle) were licensed. The vaccine was recommended routinely for children at 24 months of age and for children at 15 months of age enrolled in child care facilities. The vaccine was not consistently immunogenic in children <18 months of age.
Sept 1, 1984	The costs of hepatitis B vaccine and its administration became a covered benefit under Medicare Part B.
July 1983	Two enhanced pneumococcal polysaccharide vaccines were licensed (Pneumovax 23 by Merck on July 11 and Pnu-Imune 23 by Lederle on July 21). These vaccines included 23 purified capsular polysaccharide antigens of <i>Streptococcus pneumoniae</i> and replaced the 14-valent polysaccharide vaccine licensed in 1977.
1981	The first hepatitis B viral vaccines, developed by Merck and also by the Pasteur Institute, were licensed. Both had independently developed plasma-based hepatitis B viral vaccines.
Nov 23, 1981	Quadrivalent groups A, C, Y, and W-135 (Menomune A/C/Y/W-135 by Connaught) meningococcal vaccine was licensed. Because this and other polysaccharide meningococcal vaccines were found to induce a relatively poor immune response in children younger than two years and not able to elicit long-term immunologic memory, their use was limited to persons 2 years of age and older.
July 1, 1981	The costs of pneumococcal vaccine and its administration became a covered benefit under Medicare Part B.
May 8, 1980	The World Health Assembly certified the world free of naturally-occurring smallpox.
1980	Rabies human diploid-cell vaccine (Imovax Rabies by Mérieux and Wyvac by Wyeth) were licensed.
1979	The RA 27/3 (human diploid fibroblast) strain of rubella vaccine (Meruvax II by Merck) was licensed; all other strains were discontinued.
1979	The last cases of wild type 1 poliovirus occurred in the U.S. among unvaccinated Amish persons and members of other religious groups who did not accept vaccination. The source of the outbreak was determined to have been brought over to the U.S. from the Netherlands by members of an unvaccinated religious group.
Jan 3, 1978	Yellow fever vaccine (YF-Vax by Connaught) was licensed in the U.S.
Jan 3, 1978	Monovalent group A (Menomune-A by Connaught), group C (Menomune-C by Connaught) meningococcal vaccines, and a bivalent vaccine for both groups A and C (Menomune-A/C by Connaught) were licensed.
Nov 21, 1977	The first pneumococcal vaccine was licensed, containing 14 serotypes (of the 83 known serological groups) that comprised 80% of all bacteremic pneumococcal infections in the U.S.
Oct 26, 1977	The last case of naturally-acquired smallpox occurred in the Merca District of Somalia.
1977	Joseph A. Califano, Jr., Secretary of the Dept of Health, Education, and Welfare (later Health and Human Services) launched the National Childhood Immunization Initiative with a goal of achieving 90% vaccination levels among all children.
1976	The age for routine vaccination with MMR vaccine was changed from 12 months to 15 months.
Apr 2, 1974	The first monovalent (group C) meningococcal polysaccharide vaccine (Merck) was licensed.
1974	The Expanded Programme on Immunization was created within WHO. in response to poor immunization levels in developing countries (less than 5% of children in 1974). The following vaccines are used by the Expanded Programme on Immunization: BCG, polio, DTP, measles (often MMR), yellow fever (in endemic countries), and hepatitis B.
July 18, 1973	Measles and mumps virus vaccine, live (M-M-Vax by Merck) was licensed.
1972	The Division of Biologics Standards was transferred from NIH to FDA and renamed the Bureau of Biologics. It was responsible for the regulation of all biologics, including serums, vaccines, and blood products.

Apr 22, 1971	Combined measles, mumps, and rubella vaccine (MMR by Merck) as well as combined measles and rubella vaccine (M-R-Vax by Merck) were licensed; the vaccine was developed by Maurice Hilleman and colleagues at Merck.
1971	CDC recommended discontinuation of routine vaccination for smallpox in the U.S. following a greatly reduced risk of disease.
1969	Three rubella virus strains were licensed in the U.S.: HPV-77 strain grown in dog-kidney culture (Rubelogen by Parke-Davis); HPV-77 grown in duck-embryo culture (Meruvax by Merck); and Cendehill strain grown in rabbit-kidney culture (Cendevax by RIT-SKF, and Lirubel and Lirutrin by Dow).
1968 - 1969	The "Hong Kong" influenza pandemic, caused by an H3N2 influenza virus, resulted in roughly 34,000 deaths in the U.S.
1968	A second live, further attenuated measles virus vaccine (Attenuvax by Merck, based on the Moraten strain, derived from the Edmonston strain) was licensed.
1967	The Global Smallpox Eradication Program was launched by WHO. During the first year of the program, 44 countries, 31 of which had endemic smallpox, reported 217,218 cases.
Dec 28, 1967	Mumps virus vaccine live (MumpsVax by Merck) was licensed. The vaccine was developed by Maurice Hilleman who isolated a wild type virus from his daughter, Jeryl Lynn, who was recovering from mumps. It became known as the Jeryl Lynn strain of mumps virus.
1966	The World Health Assembly called for global smallpox eradication.
1966	CDC announced the first national measles eradication campaign. Within 2 years, measles incidence had decreased by more than 90% compared with prevaccine-era levels.
1966	The rubella virus was attenuated by Paul Parkman and Harry Meyer, Jr.
1965	Bifurcated needle for smallpox vaccine introduced
1965	Live, further attenuated measles virus vaccine (Lirugen by Pitman Moore-Dow based on the Schwarz strain, derived from the Edmonston strain) was licensed in the U.S. The recommended age for routine administration was changed from 9 to 12 months of age.
1964	A rubella epidemic swept the U.S. resulting in 12.5 million cases of rubella infection, an estimated 20,000 newborns with congenital rubella syndrome (CRS), and excess fetal and neonatal deaths in the thousands.
1964	The Immunization Practices Advisory Committee (ACIP) to the U.S. Public Health Service was formed to review the recommended childhood immunization schedule and note changes in manufacturers' vaccine formulations, revise recommendations for the use of licensed vaccines, and make recommendations for newly licensed vaccines.
June 25, 1963	Trivalent oral polio vaccine was licensed. The vaccine development began in 1957 by Albert Sabin to improve upon the killed Salk vaccine.
1963	The Federal Immunization Grant Program was established. The grants, authorized under section 317 of the Public Health Service Act, were made to states to provide funds to purchase vaccines and to support basic functions of an immunization program. The only vaccines available at the time were DTP, polio, and smallpox.
Mar 21, 1963	The first live virus measles vaccine (Rubeovax by Merck) was licensed. Other live virus measles vaccines were eventually licensed (M-Vac by Lederle, Pfizer-vax Measles-L by Pfizer, and generic vaccines by Lilly, Parke Davis, and Philips Roxane).
1963	Inactivated measles vaccine (Pfizer-vax Measles-K by Pfizer and a generic vaccine by Lilly) were licensed in the U.S. These vaccines were eventually withdrawn from the U.S. market in 1967.
1962	President John F. Kennedy signed the the Vaccination Assistance Act into law. It allowed the CDC to support mass immunization campaigns and to initiate maintenance programs.
Mar 27, 1962	Oral polio vaccine type 3 was licensed in the U.S., as well as the trivalent product.
1961	Oral polio vaccine types 1 and 2, developed by Dr. Albert Sabin and grown in monkey kidney cell culture, were licensed for use in the U.S.
1957 - 1958	The "Asian" influenza pandemic, caused by an H2N2 influenza virus, resulted in an estimated 70,000 deaths in the U.S. alone.
1955	The Polio Vaccination Assistance Act was enacted by Congress, the first federal involvement in immunization activities. It allowed Congress to appropriate funds to the Communicable Disease Center (later the Centers for Disease Control and Prevention) to help states and local communities acquire and administer vaccine.
1955	The Cutter polio vaccine incident began on April 25, 1955, when polio was reported in a vaccine recipient. One day later, five more cases were reported. All cases had received vaccine produced by Cutter Laboratories. Polio was reported in 94 vaccinees and in 166 close contacts of vaccinees. On April 27, the Laboratory of Biologics Control requested that Cutter Laboratories recall all vaccine and the company did so immediately. On May 7, the Surgeon General recommended that all polio vaccinations be suspended pending inspection of each manufacturing facility

	and thorough review of the procedures for testing vaccine safety. The investigation found that live polio virus had survived in two batches of vaccine produced by Cutter Laboratories. In 1955, as a result of the Cutter Incident, the Laboratory of Biologics Control was raised to division status within NIH, to strengthen and expand its biologics control function. Large-scale polio vaccinations resumed in the fall of 1955.
Apr 12, 1955	The first polio vaccine was licensed -- an inactivated poliovirus vaccine (IPV) pioneered by Dr. Jonas Salk.
1954	The Nobel Prize in Medicine was awarded to John Enders, Thomas Weller, and Fredrick Robbins for their discovery of the ability of poliomyelitis viruses to grow in tissue cultures.
1954	John Enders and Thomas Peebles isolated the measles virus in cell culture.
1953	Tetanus and diphtheria toxoids (adult formulation) was first licensed in the U.S., after the concentration of diphtheria toxoid was reduced.
May 22, 1953	Yellow fever vaccine (Merrell National Labs) was first licensed in the U.S.
July 16, 1952	Heat-phenol inactivated typhoid vaccine by Wyeth was licensed.
1952	The worst recorded polio epidemic in U.S. history occurred with 57,628 reported cases
1949	Diphtheria and tetanus toxoids and pertussis (DTP) was licensed.
1949	The last case of smallpox in the U.S. was reported; however, it took another two decades before the disease was eradicated globally.
1947	Combination diphtheria and tetanus toxoids for pediatric use was first licensed in the U.S.
1945	Inactivated influenza vaccine was first licensed in the U.S.
1945	K Habel and John Enders isolated the mumps virus.
1944	The Public Health Services Act of 1944 was enacted, consolidating all legislation affecting the functions of the Public Health Service.
1943	Penicillin first became mass-produced. This medical miracle, rediscovered by Alexander Fleming in 1928, was capable of attacking many types of disease-causing bacteria. It played a vital role in treating infected wounds during World War II.
1942	Influenza A/B vaccine was introduced to the Armed Forces Epidemiological Board. The influenza vaccine was licensed in 1945 and, following the war, was also used for civilians.
1942	Hepatitis A and B viruses were first differentiated.
1938	President Franklin D. Roosevelt, a victim of polio, founded the National Foundation for Infantile Paralysis, later known as the March of Dimes.
1937	An adsorbed form of tetanus toxoid was first licensed in the U.S.
1937	The Division of Biologics Control was formed within the National Institute of Health. Much later, in 1972, the Division was transferred to the FDA.
1935	A live yellow fever vaccine (17D) was first licensed. The development of the chorioallantoic membrane for culturing viruses had led to its development.
1930	The Hygienic Laboratory changed its name to the National Institute (singular) of Health and authorized the establishment of fellowships for biological and medical research.
1930	Cell culture was developed and shown to be able to grow virus, thus paving the way for the subsequent production of viral vaccines.
1928	The first iron lung was used to preserve breathing function in patients with acute polio.
1927	Bacille Calmette-Guerin (BCG) vaccine was first used in newborns, having been developed by Albert Calmette and Camille Guérin in 1921. BCG (live-attenuated <i>Mycobacterium bovis</i> BCG) represented the only vaccine against tuberculosis. It has become the most widely administered of all vaccines in the WHO Expanded Programme for Immunization, but has been estimated to prevent only 5% of all potentially vaccine-preventable deaths due to tuberculosis.
1923	Diphtheria toxoid was licensed; prepared from the inactivated bacterial toxin that has lost its toxicity but retains its antitoxin producing properties. In 1924, Gaston Ramon discovered diphtheria toxoid. Along with the discovery of antitoxins, Ramon uncovered the role of adjuvant substances of immunity.
1918	The "Spanish flu" influenza pandemic was responsible for at least 50 million deaths worldwide, with about 675,000 deaths in the U.S. This virus was unusual because it spread so quickly, was so deadly, and exacted its worse toll among the young and healthy. About one-third of the world's population (~500 million people) were infected.
1915	Pertussis vaccine, a suspension of inactivated <i>Bordetella pertussis</i> cells, was licensed. Inactivated vaccines were prepared with a microorganism or virus that had been killed, usually with a chemical such as formaldehyde.

1914	Typhoid vaccine was first licensed in the U.S.
1914	Rabies vaccine was first licensed in the U.S.
1914	Tetanus toxoid was introduced following the development of an effective therapeutic serum against tetanus by Emil Von Behring and Shibasaburo Kitasato.
1908	The first county health departments in the U.S. were formed.
1906	The Pure Food and Drugs Act was formed, prohibiting interstate commerce in misbranded and adulterated foods, drinks, and drugs.
April 5, 1902	The Biologics Control Act was formed. It included the regulation of vaccine and antitoxin producers and required both licensing and inspections of manufacturers. The standards imposed by the 1902 Act resulted in bankruptcy for one-third of the companies manufacturing antitoxins and vaccines while benefiting the manufacturers already in compliance. Ten firms held licenses with the Laboratory of Hygiene following the 1902 Act.
1901	In St. Louis, 13 children died of tetanus-contaminated diphtheria antitoxin. In the autumn of 1901, nine children in Camden, New Jersey, died from tainted smallpox vaccine. Efforts to ensure the purity of biological treatments by government oversight followed with the Biologics Control Act of 1902.
1901	The first Nobel Prize for Physiology and Medicine was awarded to Emil von Behring for his work on the development of a diphtheria antitoxin (later known as antiserum).
1897	Plague vaccine was introduced, following the preparation of anti-plague horse serum at the Pasteur Institute by Alexandre Yersin. After demonstrating protection from disease in immunized animals, Yersin went to China with the vaccine to protect humans during a plague epidemic.
1896	Cholera and typhoid vaccines were first developed.
1893	City and state public health departments began mass production of diphtheria antitoxin, following its introduction in European laboratories.
1888	The Pasteur Institute was established as a rabies treatment center as well as an infectious diseases research and training institute.
1888	The diphtheria toxin was discovered by Emile Roux. Passive serum therapies were developed through the scientific contributions of many, including Emil Von Behring who developed the first effective therapeutic serum against diphtheria and Paul Ehrlich who developed enrichment and standardization protocol, which allowed for an exact determination of quality of the diphtheria antitoxins.
1887	Joseph Kinyoun established one of the country's first bacteriological laboratories in the Marine Health Service Hospital on Staten Island, NY. He was director of the Laboratory of Hygiene, which moved to Washington, D.C., in 1891. Kinyoun brought the latest techniques such as the procedure for preparing diphtheria antitoxin back from his visits to Europe.
1885	Louis Pasteur first used rabies vaccine in humans.
1884	The first live attenuated viral vaccine (rabies) was developed by Louis Pasteur, using dessicated brain tissue inactivated with formaldehyde.
1882	Robert Koch identified the tubercle bacillus as the cause of tuberculosis, subsequently called Koch's bacillus.
1881	Louis Pasteur and George Miller Sternberg almost simultaneously isolated and grew the pneumococcus organism.
1879	Louis Pasteur created the first live attenuated bacterial vaccine (chicken cholera)
1877	Louis Pasteur proposed The Germ Theory of Disease.
1798	Edward Jenner published his work on the development of a vaccination that would protect against smallpox. Two years earlier, in 1796, he had first speculated that protection from smallpox disease could be obtained through inoculation with a related virus, vaccinia or cowpox. He tested his theory by inoculating eight-year-old James Phipps with cowpox pustule liquid recovered from the hand of a milkmaid, Sarah Nemes.
1798	The Marine Health Service was established in 1798 as the nation's first public health agency. It provided hospital care for merchant seamen and protected port cities against diseases such as smallpox, cholera, and yellow fever.
1721	Variolation was introduced to Great Britain.
1100s	The variolation technique was developed, involving the inoculation of children and adults with dried scab material recovered from smallpox patients. Variations of variolation have been noted in Turkey, Africa, China, and Europe.
400 BC	Hippocrates described mumps, diphtheria, epidemic jaundice, and other conditions

Fake data, untouchable men and guilty women at ICR London

by Leonid Schneider

13-16 minutes

My [previous article](#) covered manipulated western blot data in the papers authored by [Paul Workman](#), president and CEO of the huge **Institute of Cancer Research (ICR)** in London, part of University of London. It seems now, with nobody being above him, Workman was investigating himself, and found (at the present count) two female colleagues guilty of placing fake data into his papers, primarily the ICR emeritus professor [Ann Jackman](#). One paper was retracted, another received an outrageous correction. There, the paper's first author, Workman's former PhD student and now ICR Professor [Udai Banerji](#), laid all the blame with Jackman, and then reproduced the offending western blot in what the journal declared to be reliable manner, so the findings of a paper are not affected despite western blot some unreliable women were accused to have faked.

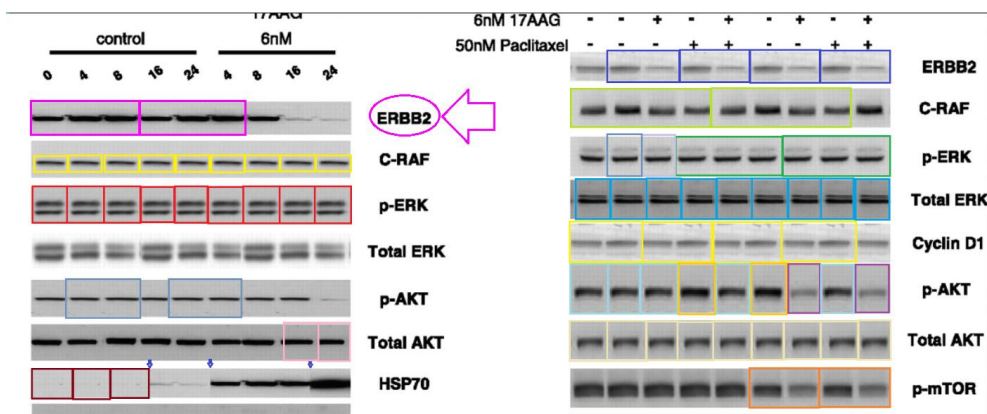
If this sounds bizarre: ICR's troubles with research integrity and basic ethics did not start with Workman. The previous CEO, who now left for UCSF in USA, [Alan Ashworth](#), and his former right-hand man, since 2017 ICR professor [Chris Lord](#), have their own impressive, but hitherto ignored, common record on PubPeer. Not that anyone cares, after all these are gentlemen.

This is how the research charity ICR wants to cure cancer using your donations. By faking western blots and who knows what other data, and run clinical trials based on this. The ICR men behind that get richer and richer, but will any cancer patients be helped with such rigged research?



Spot the liar! Photo: [ICR](#)

The by far worst Workman co-authored paper presented in [my article](#) was [Sain et al, Molecular Cancer Therapeutics 2006](#). It was so ridiculously fake that the US publisher, the cancer research society AACR, had no other option but to retract it. Just look at its Figure 6 (there is much more [on PubPeer](#)):



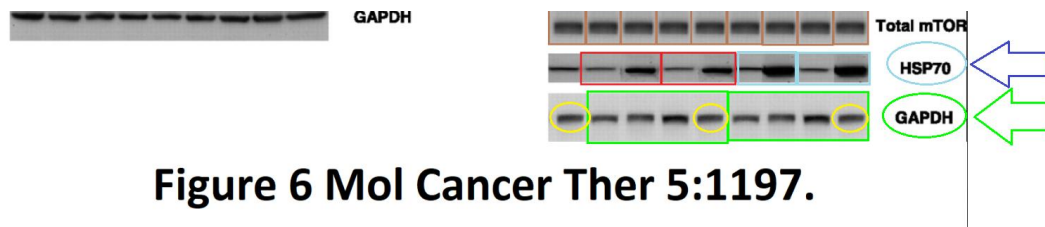


Figure 6 Mol Cancer Ther 5:1197.

This is the [retraction notice](#), published in the journal's September 2018 issue:

“[This article](#) (1) is being retracted at the request of the authors. The work is in two main parts. The first part is a description of the relevant characteristics of the human ovarian cancer cell lines used and an analysis of the efficacy of the combination of the HSP90 inhibitor 17-AAG with paclitaxel and carboplatin. The latter part shows the effect of the single agents and drug combinations on HSP90 client proteins and downstream effectors. All of the experiments in the article were carried out in the laboratory of the senior author A.L. Jackman. It has been brought to our attention that in the second part of the article, Figs. 5A, 5B, 6, 7, and 8 contained inappropriately assembled Western blots. N. Sain performed the experiments and processed the data and has taken primary responsibility for the flawed figures. The authors wish to sincerely apologize to the scientific community and deeply regret any inconveniences or challenges resulting from the publication and subsequent retraction of this article”.

That first author Nivedita Sain doesn't work at ICR anymore, likely since around a decade. It is not clear how the inquisitors around Workman were able to make her admit her guilt, maybe Sain actually has no clue what she is being accused of. The other woman made responsible for data fraud is ICR emeritus professor Jackman, who never replied to my emails. She did post a comment [on PubPeer](#) in February 2018:

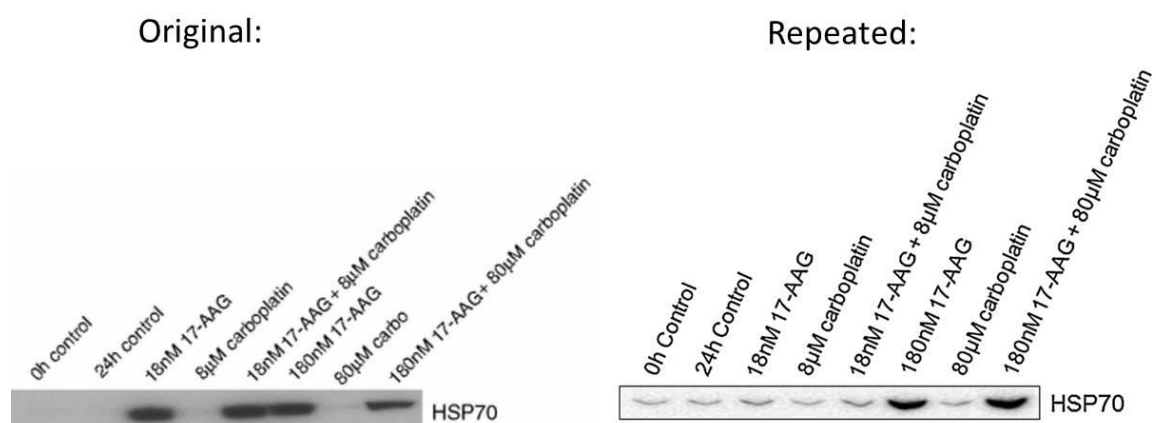
“We have noted these comments and are investigating”

The take-home message from this retraction notice: Workman had nothing to do with that paper.

He is however corresponding author on the work by his former PhD student Banerji: [Banerji et al, *Cancer Chemotherapy and Pharmacology*, 2008](#), and its Figure 2 is utterly fake. But because the paper also features Sain and Jackman as co-authors, this [Correction](#) was issued on September 1st:

“The corresponding author of the original article has informed us of concerns about the immunoblots in Fig. 2 which were carried out in the collaborating laboratory of Professor Ann Jackman. The experiment has been replicated twice in the Workman laboratory and the findings remain the same. The authors have provided the original blots and the corrected version for Fig. 2 and this has been included in the latest online HTML and PDF versions of the article. The change does not affect the Figure Legend or main text of the article. The authors regret this error.”

Basically, Banerji was the inquisitor delegated to find the culprits for fake data in his paper (Sain and Jackman), and to replicate the fake results, to find out that the findings “remain the same”. I was joking in my article that the authors will probably go back and reproduce the results from 10 years ago, and this is exactly what they claim to have achieved, faithfully. Except that they didn't, a PubPeer user [demonstrates](#) that the new blot shows quite different results as the previous one:



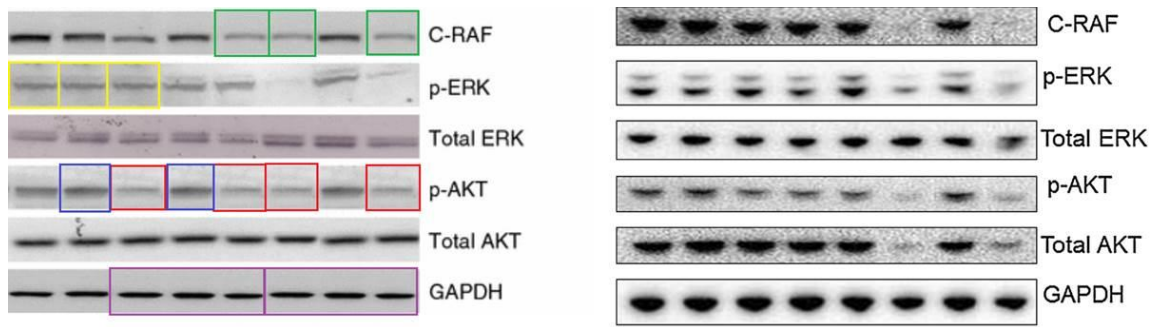


Figure 2 Cancer Chemother Pharmacol 62:769.

Left: old fake figure, blamed on Jackson. Right: 10 years later Banerji-newly generated figure, which we must accept as showing exactly same results. Except that it isn't, eg [PubPeer comment](#): "there is no longer inhibition of HSP70 function at the IC50 concentration of 17-AGG".

The journal has two editor-in-chief, both men. The one responsible for papers from Europe is [Étienne Chatelut](#), from INSERM in France. I really don't know anymore, is this a cultural peculiarity for French academics to publicly endorse data manipulation? But blaming it all on female collaborators is a new one for sure.

But maybe Workman was indeed a victim of some fraudulent females? After all, look what trouble the employment of females brought to ICR: [Nazneen Rahman resigned](#) as ICR professor after being accused of bullying by no less than 45 of her colleagues and losing her Wellcome Trust funding as the result. Incidentally, Rahman's former PI and ICR professor [Michael Stratton](#), was [accused of bullying himself](#), in his current position as director of Sanger Institute. It would be interesting to know the full scope of the Rahman scandal, and who exactly led and supervised the ICR investigation into her alleged bullying. After all, we know that Banerji and Workman investigated themselves and found Ann Jackson and Nivedita Sain guilty. ICR is a strange place.

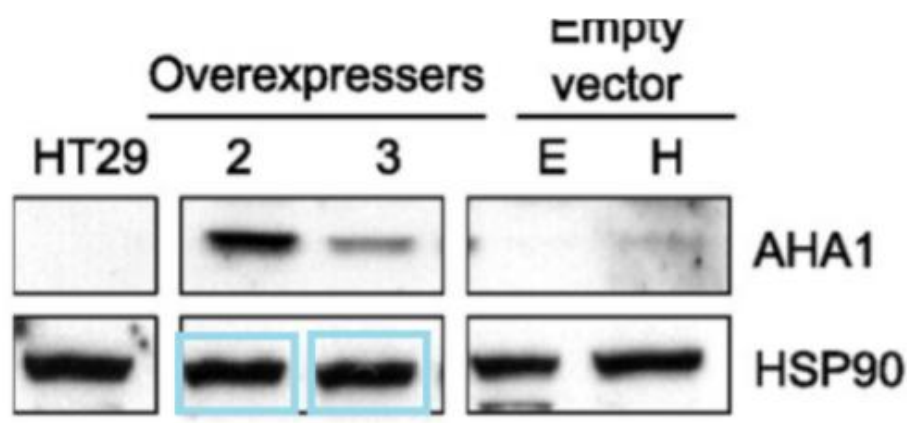
The named person in charge of Workman et al investigation is ICR professor and academic dean [Clare Isacke](#), she of course never replied to my emails. On 13 February she wrote to a colleague, who complained of receiving emails from the data integrity sleuth [Clare Francis](#), as well as [this offensive link](#):

“Meanwhile, yes I am fully aware of the Clare Francis emails and the PubPeer postings and all the allegations either have been or are being fully investigated. I am the ICRs “named person” so am in charge of the investigations”

Maybe Isacke is simply afraid to displease her boss she is supposed to investigate. After all, it is the ICR CEO Workman who makes the final decision in misconduct investigations, as per protocol. And women have to tread carefully at ICR, it seems.

Now, what about Workman’s other papers then, which feature neither Sain nor Jackman? I presented some in my [previous article](#), and these were untainted by their presence. Maybe this is why Isacke and ICR chose to ignore that evidence? Or maybe Workman’s loyal inquisitors are about to smoke out another female saboteur, who knows.

Here another paper [from PubPeer](#), corresponding last author Workman, again on the topic of HSP90 inhibitors: [Holmes et al, Cancer Research 2008](#). The band cloning pattern resembles the one Sain and Jackson were pronounced guilty of.



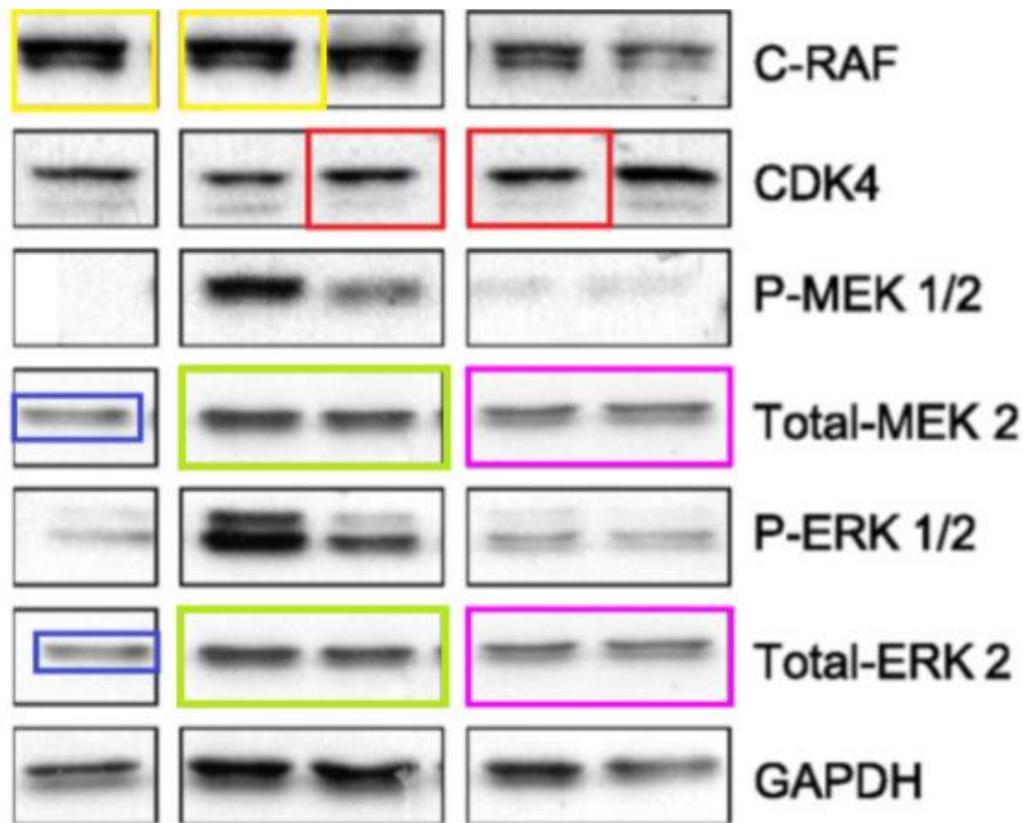


Figure 2B Cancer Res 68:1188.

If this will ever be corrected, we can probably expect Jessica Holmes to admit full responsibility. Which of the many female co-authors will take the fall for Workman's paper [Sharp et al 2007](#), in the same AACR journal *Cancer Research*?

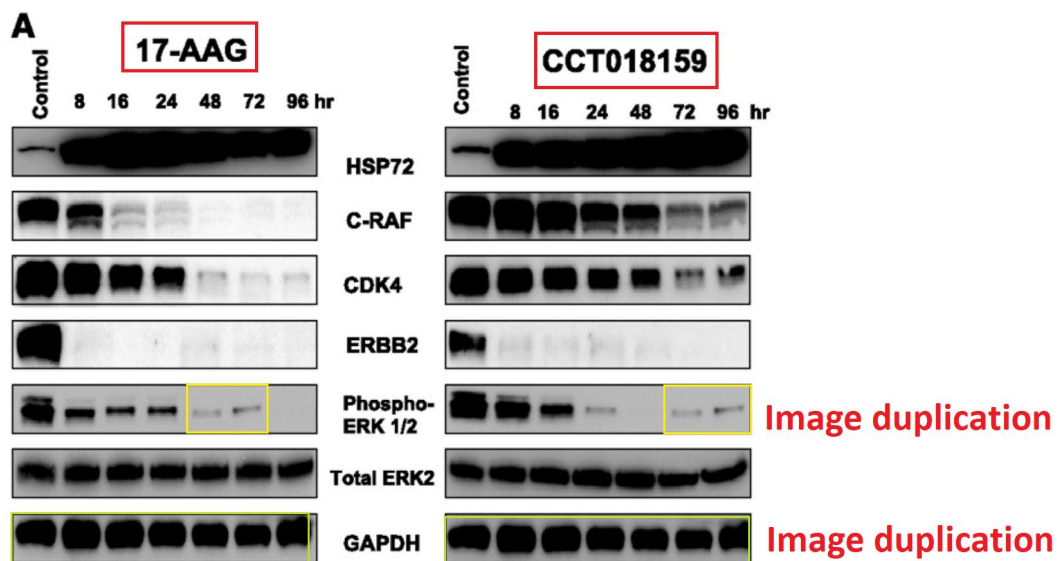


Figure 3A Cancer Res 67:2206.

And how about this paper, where Workman is merely co-author though, [Rayter et al Oncogene 2008](#)?

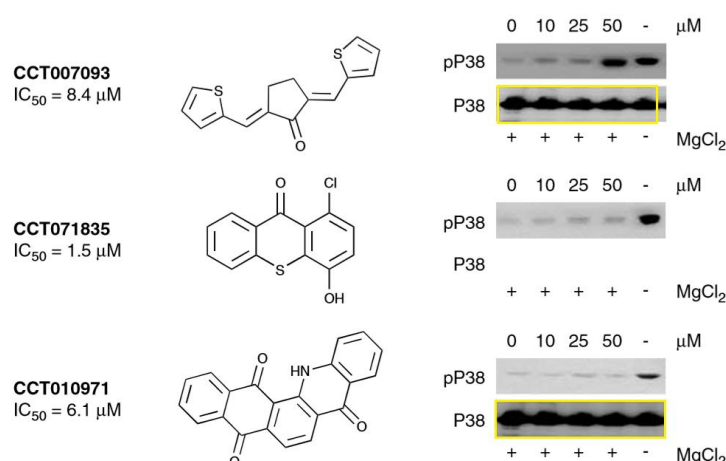


Figure 3 Effect of chemical inhibitors on PPM1D phosphatase activity. Western blots are shown detailing for each compound the effect of increasing concentration (10–50 μM) of inhibitors on phosphorylation of full-length recombinant P38 (at approximately 50 kDa) in the presence of rPPM1D and MgCl₂ in an *in vitro* assay. In each case, total P38 was used as a loading control.

Figure 3 Oncogene 27:1036.

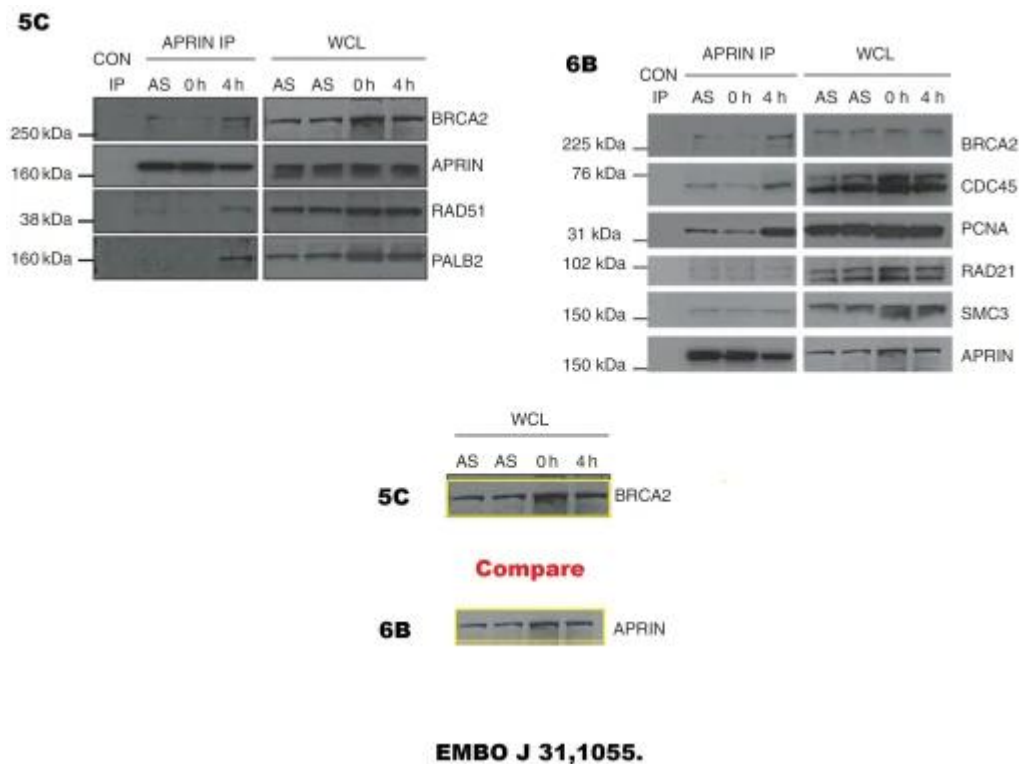
The last two authors here are [Chris Lord](#) and [Alan Ashworth](#). The latter became ICR president [in January 2011](#), and after a brief tenure of mere 3.5 years Ashworth moved in 2014 to San Francisco, California, to head the Helen Diller Family Comprehensive Cancer Center, as Senior Vice President for Cancer Services at UCSF. Not everyone at ICR was sad about Ashworth's leaving, there were apparently numerous complaints "of all types", as an inside source indicated, with the hogging a newly bought supercomputer for his own sequencing projects being a minor issue. Let it be said that the alleged bully Rahman used to work in Ashworth's department. Workman took over the rule over ICR from Ashworth [in 2014](#), and many saw him as a pleasant change from Ashworth, in many respects.

Doing Lord's work

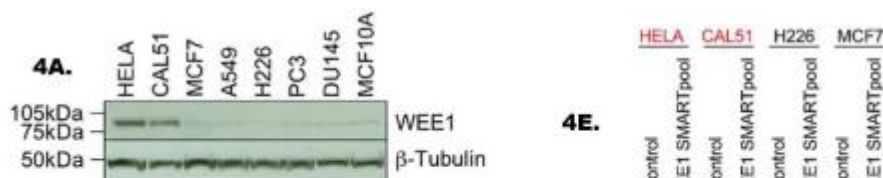
Lord used to be Ashworth's postdoc, and he was that excellent in his research under Ashworth, that he was "internally promoted", i.e., appointed as principal investigator outside of all calls and competition, normally mandated by ICR guidelines. In

2017, Lord was made professor. Maybe he will be now tasked with investigating his own papers? There is certainly plenty to do.

Ashworth's claim to fame is in having discovered the *BRCA2* oncogene. In fact, in his hands (watched over by Lord) the protein BRCA2, when requested by experimental strategy, can even mutate into different proteins, like APRIN. Which kind of proves the papers central claim in the title of [Brough et al EMBO J 2012](#): that "*APRIN is a cell cycle specific BRCA2-interacting protein required for genome integrity and a predictor of outcome after chemotherapy in breast cancer*".



Here another duplication from Lord and Ashworth paper, in [Iorns et al PLOS One 2009](#), and the loading control doesn't match any of the two separate experiments it is made to stand for. Where did it originally come from? Which samples does it really show? Does it matter?



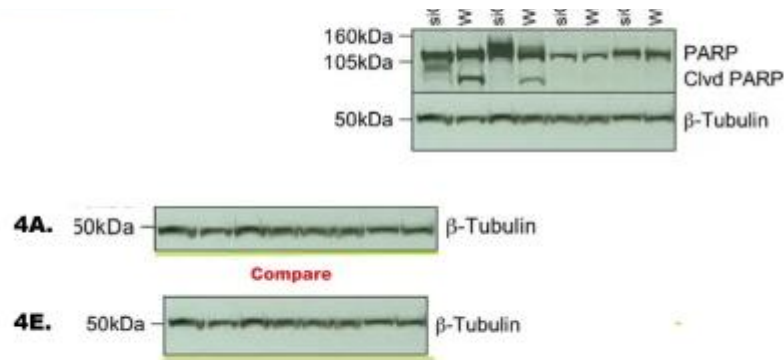


Figure 4 Plos One 4,e5120.

Or look at this interesting study Ashworth and Lord published in *Cancer Research* 7 years ago: [Martin et al 2011](#). Incidentally, Ashworth is member of the [AACR board of directors](#), which might interfere with this publisher's investigation of his and likely also his ICR successor Workman's (other) papers. In that paper, a novel cancer cure approach was established by specific targeting of the enzyme PINK using RNA interference (siRNA), which could be further potentiated by duplicating loading controls!

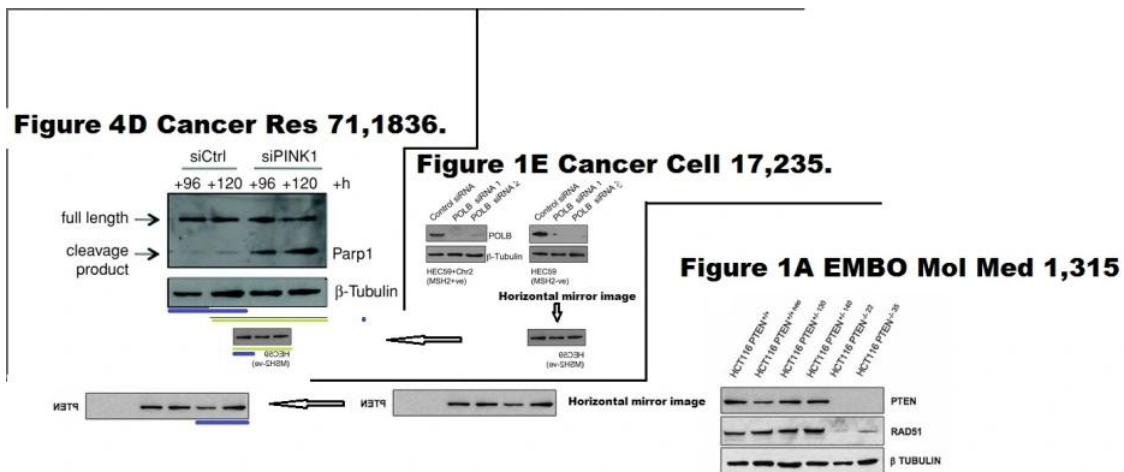


Figure 4E Cancer Res 71,1836.

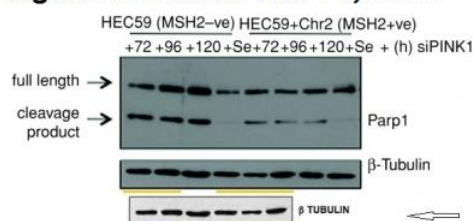
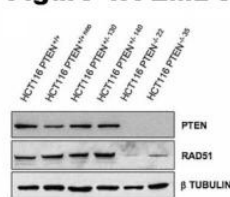


Figure 1A EMBO Mol Med 1,315.

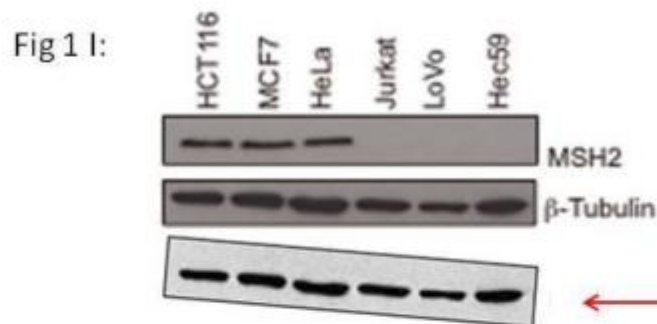


Cancer Res 71 1836

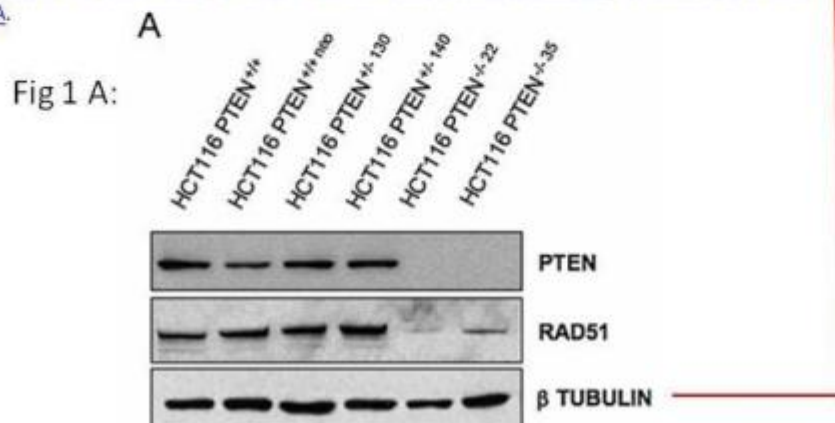
Of course it is not clear how translatable this loading control

duplication is in the clinic, in patients. It works however reliably in other papers by Lord and Ashworth, even between publications showing utterly different cell lines, here [Martin et al 2009](#) and [Mendes-Pereira et al 2009](#), both published in *EMBO Molecular Medicine*:

[EMBO Mol Med.](#) 2009 Sep;1(6-7):323-37. doi: 10.1002/emmm.200900040.
Methotrexate induces oxidative DNA damage and is selectively lethal to tumour cells with defects in the DNA mismatch repair gene MSH2.
[Martin SA](#)¹, [McCarthy A](#), [Barber LJ](#), [Burgess DJ](#), [Parry S](#), [Lord CJ](#), [Ashworth A](#).

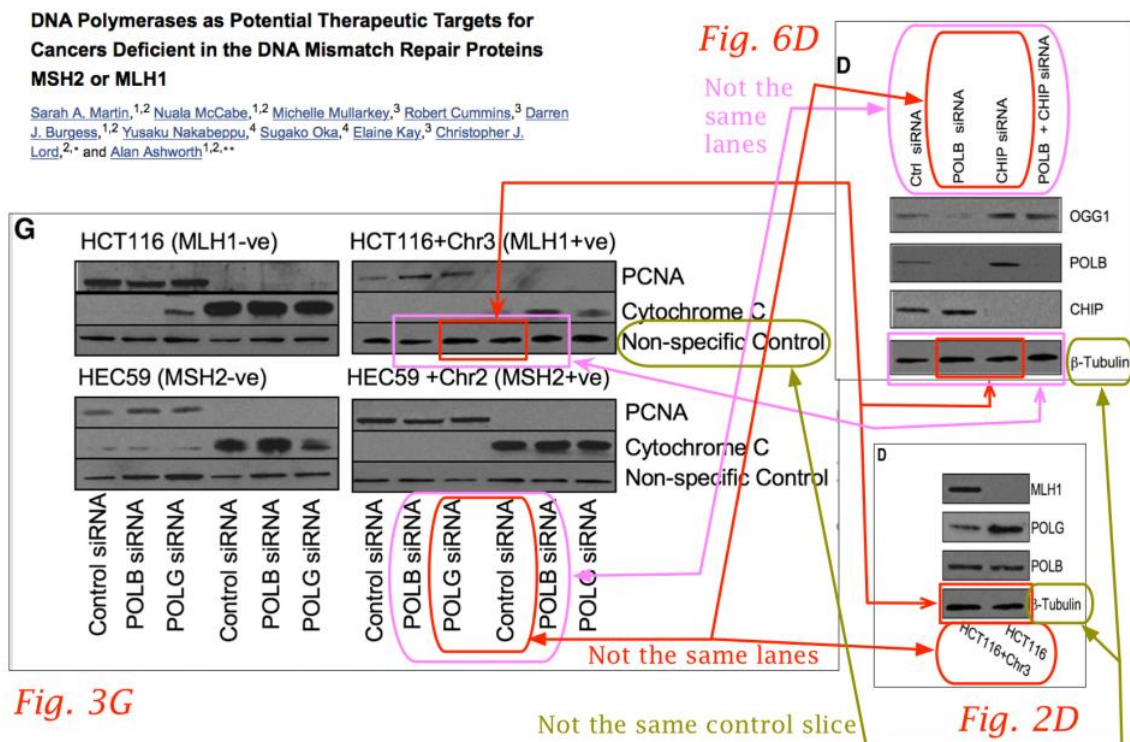


[EMBO Mol Med.](#) 2009 Sep;1(6-7):315-22. doi: 10.1002/emmm.200900041.
Synthetic lethal targeting of PTEN mutant cells with PARP inhibitors.
[Mendes-Pereira AM](#)¹, [Martin SA](#), [Brough R](#), [McCarthy A](#), [Taylor JR](#), [Kim JS](#), [Waldman T](#), [Lord CJ](#), [Ashworth A](#).



Incidentally, Ashworth is [EMBO](#) member, which makes the issue of the above 3 papers in EMBO Press even more embarrassing. There is an even more interesting paper by Lord and Ashworth, published as [Martin et al 2010](#) in *Cancer Cell*, which means this paper is safe from retraction or correction for all eternity, because this is Cell Press. There is plenty [on PubPeer](#), posted already 3 to 5 years ago, and nobody, absolutely nobody cares. Look at this beauty, this is how the authors intended to cure cancer by inhibiting DNA polymerases *in vitro* while copy-

pasting western blot bands *in silico*:



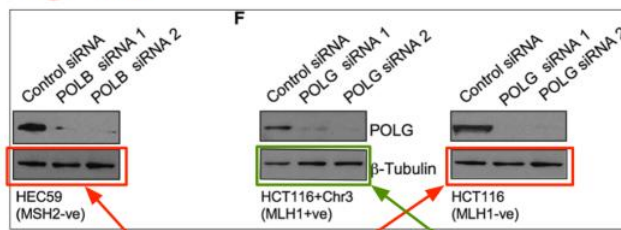
It's all just loading controls, innit? Who needs those anyway? It is so cumbersome to fret about loading controls when you achieved your perfect gel image, nicely showing an increase in signal of a certain protein. All you had to accidentally do was to load just a tiny amount more to that well. Or less, if your experimental strategy predicted a decrease of that protein in that sample. It is all perfectly acceptable when you know anyway which results to expect, right? Especially if you work at ICR, where cancer is being daily conquered by superior Englishmen intelligence?

This is why it is perfectly OK to make up some fake loading control in Photoshop to satisfy some silly publishing criteria and to placate peer reviewers. It's all illustrations anyway, as ICR scientists explained in that correction above: it is "Figure Legend or main text of the article" which matter. Not the figures.

Hence also this, in the same [Martin et al Cancer Cell 2010](#) paper. If you have an issue with that creative band reuse, try

publishing in *Cancer Cell* yourself, then come back complaining.

Fig. 1E,F

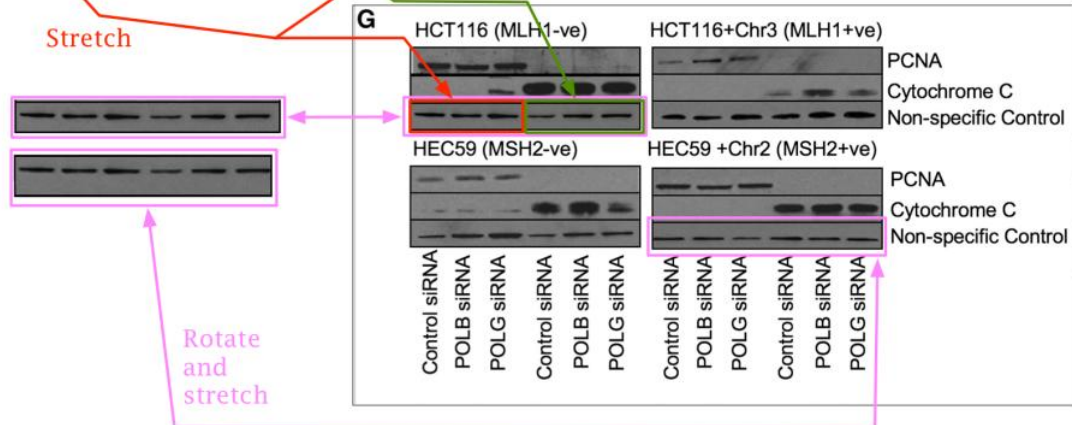


DNA Polymerases as Potential Therapeutic Targets for Cancers Deficient in the DNA Mismatch Repair Proteins MSH2 or MLH1

Sarah A. Martin,^{1,2} Nuala McCabe,^{1,2} Michelle Mullarkey,³ Robert Cummins,³ Darren J. Burgess,^{1,2} Yusaku Nakabeppu,⁴ Sugako Oka,⁴ Elaine Kay,³ Christopher J. Lord,^{2,*} and Alan Ashworth^{1,2,*}

Observe numerous mismatches between labelled cells and also labelled lanes

Fig. 3G

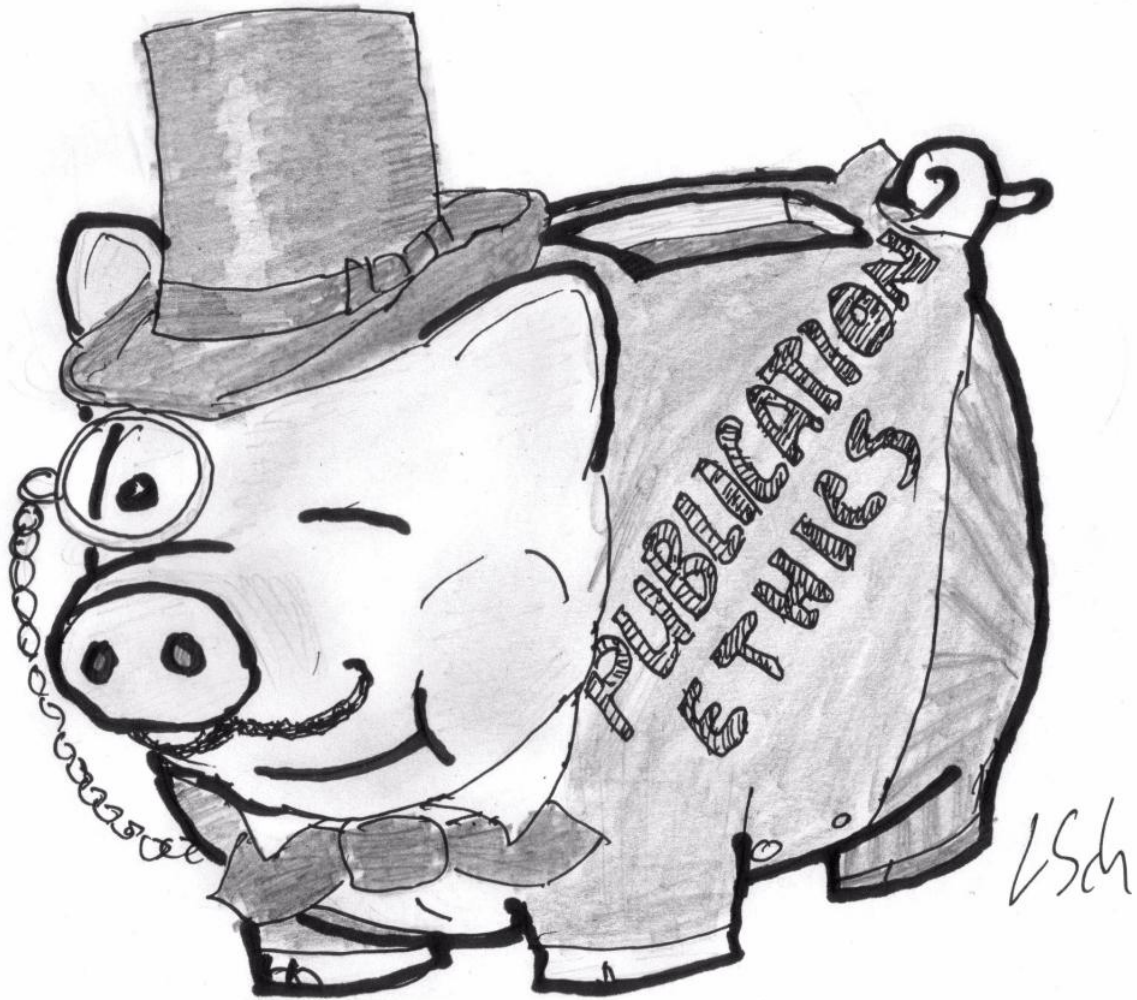


[Dr Sarah Martin](#) is now senior lecturer at Bart's Cancer Institute at Queen Mary University London. 3 years ago, a [PubPeer user](#) tried to report the issues to the institution, and was dismissed as “a malicious email campaign”. Which means, ICR male elite will have to find another woman to take the blame for that Photoshop creativity.

Professor Lord serves as a member of the [Athena SWAN](#) steering group, as we are educated on his website, to advance “the careers of women in science, engineering, technology, maths and medicine through excellent employment practice in higher education”. Maybe Lord learned it from his boss: Ashworth is remembered at ICR for having dedicated much of his attention to women in science. In any case, obviously ICR could not trust a woman with the important task of Athena SWAN.

There is more [by Lord and Ashworth](#) on PubPeer, and also [by Workman](#), who as you probably already figured out, is

responsible for reacting to investigate his as well as Lord and Ashworth papers. Good luck there. Also, the sheer amount of evidence precludes any meaningful external intervention, otherwise ICR would collapse or at least lose charity donations. Please give generously, it is for a good cause.



Donate!

If you are interested to support my work, you can leave here a small tip of \$5. Or several of small tips, just increase the amount as you like (2x=€10; 5x=€25). Your generous patronage of my journalism will be most appreciated!

€5.00